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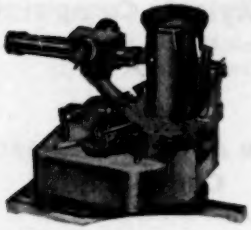

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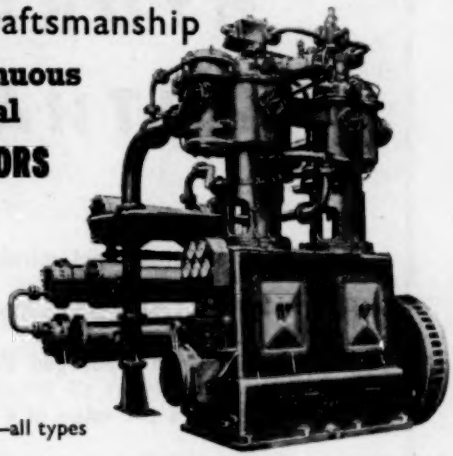

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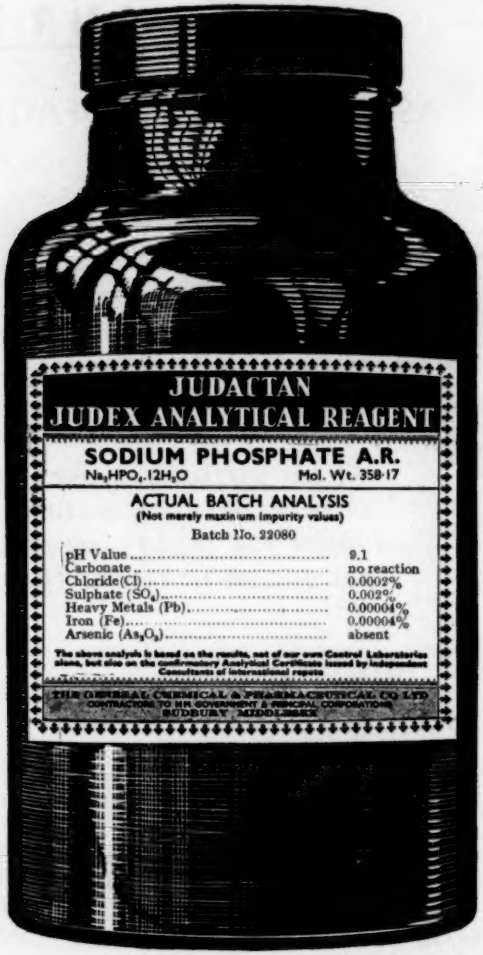

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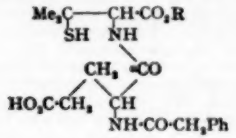
255. N-(N-*Phenylacetyl*-α-DL-*glutamyl*)-D-*penicillamine*.

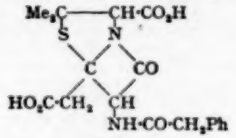
By Wilson Baker and P. G. Jones.

N-Phenylacetyl-L-glutamic acid reacts with acetic anhydride to give an optically inactive anhydro-derivative, which is doubtless 2-benzyl-4-2′-carboxyethyloxazol-5-one (IV). The α-amide (V) and the α-hydrazide (VI) of *N*-phenylacetyl-DL-glutamic acid and the γ-methyl ester of *N*-(*N*-phenylacetyl-α-DL-glutamyl)-D-penicillamine (I) are formed when the anhydro-derivative is treated with ammonia, hydrazine, and D-penicillamine methyl ester respectively.

This paper describes the synthesis of the methyl ester of *N*-(*N*-phenylacetyl-α-DL-glutamyl)-D-penicillamine (I ; R = Me). The corresponding dicarboxylic acid was obtained but only partly purified. The object in preparing these compounds was to see if they could be converted by *Penicillium notatum* or *in vivo* into antibiotics related to benzylpenicillin. The possibility exists that the central methylene group of the glutamic acid residue might undergo biological oxidation to a carbonyl group, and then condense with the SH and NH groups of the penicillamine portion of the molecule to give either a carboxymethyl-benzylpenicillin (II) or, by decarboxylation of the intermediate stage, a methyl-benzylpenicillin (III).



(I.)



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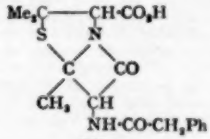
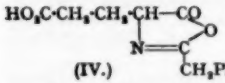


(III.)

No evidence is available to show if compounds of the type (II) or (III) would exhibit antibiotic activity, but a significant early observation made in the research laboratories of the Upjohn Company (Committee for Penicillin Synthesis Reports, C.P.S. 1944, No. 174) was that *N*-phenylacetyl-L-glutamic acid, when tested as a biological precursor of penicillin, gave preliminary results which were " sufficiently suggestive as to warrant further study." However, when compound (I ; R = H) and its methyl ester (I ; R = Me) were submitted to biological tests, no evidence of antibiotic activity was obtained.

N-Phenylacetyl-L-glutamic acid, prepared by the action of phenylacetyl chloride on L-glutamic acid in alkaline solution, was converted by the action of acetic anhydride into a crystalline, optically inactive anhydro-derivative which is readily hydrolysed by cold, aqueous sodium hydrogen carbonate, giving *N*-phenylacetyl-DL-glutamic acid. Hydration also occurs on rapid titration in the cold in aqueous dioxan, two equivalents of alkali being neutralised. Since racemisation occurred, it is most probable that the anhydro-derivative is 2-benzyl-DL-4-2′-carboxyethyloxazol-5-one (IV). Treatment of (IV) with ammonia in chloroform gave an amide which, on this assumption, is the α-amide (V) of N-phenylacetyl-DL-glutamic acid.



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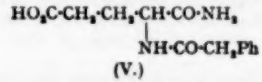

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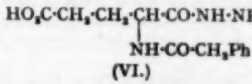

(VI.)

The α-hydrazide (VI) of *N*-phenylacetyl-DL-glutamic acid was prepared from the oxazolone (IV) by reaction with methyl alcohol and treatment of the resulting methyl ester with 96% hydrazine and also, more directly, by treating the oxazolone with hydrazine. Completely satisfactory analytical figures could not be obtained for this compound, but it readily yielded well-defined *iso*propylidene and benzylidene derivatives. The derived azide was condensed with D-pencillamine, yielding a non-crystalline product regarded as crude *N*-(*N*-phenylacetyl-α-DL-glutamyl)-D-penicillamine (I ; R = H).

The methyl ester of the hydrazide (VI) was prepared by the action of ethereal diazomethane, and characterised as *iso*propylidene and benzylidene derivatives. After conversion into the azide and condensation with D-penicillamine methyl ester, it gave a non-crystalline product which was not further investigated.

A more satisfactory result was obtained by the direct interaction of the oxazolone (IV) with D-penicillamine methyl ester. The product, the methyl ester of *N*-(*N*-phenylacetyl-α-DL-glutamyl)-D-penicillamine (I; R = Me) was again non-crystalline, but gave satisfactory analytical figures.

Experimental.

M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford.

N-Phenylacetyl-L-glutamic Acid.—This compound was first prepared by Thierfelder and Sherwin (*Z. physiol. Chem.*, 1915, **94**, 1), who obtained it with some difficulty as a solid, m. p. 123°, and it was later prepared by Shiple and Sherwin (*J. Biol. Chem.*, 1922, **53**, 472) as an uncharacterised syrup; in neither case is any yield given. As prepared by the action of phenylacetyl chloride on L-glutamic acid in alkaline solution, the product is heterogeneous and suffers considerable loss on crystallisation. The yield of pure product obtained in the present work is 38%.

To a solution of L-glutamic acid (50 g.) in water (272 c.c.) containing sodium hydroxide (27·2 g.) was added slowly and simultaneously, with stirring and cooling in ice, phenylacetyl chloride (63 g., 1·2 mols.) and a solution of sodium hydroxide (19·6 g., 1·2 mols.) in water (98 c.c.). After 2 hours the solution was extracted with ether and acidified, and the precipitated oil was washed with benzene to remove phenylacetic acid, giving an oil (61·7 g.) which slowly crystallised in a desiccator. This sticky material was dissolved in three volumes of hot water, and the solution slowly deposited *N*-phenylacetyl-L-glutamic acid (34·5 g.; m. p. 123°) which after recrystallisation had m. p. 125—126°, $[\alpha]_D^{15}$ −21° (*c*, 1·0 in water) (Found: C, 58·9; H, 5·7. Calc. for $C_{13}H_{15}O_5N$: C, 58·9; H, 5·7%). The m. p. is lowered considerably by traces of water.

2-Benzyl-DL-4-2′-carboxyethyloxazol-5-one (IV).—*N*-Phenylacetyl-L-glutamic acid (5 g.) and acetic anhydride (15 c.c.) were heated on a water-bath for 15 minutes, and the excess of acetic anhydride removed under diminished pressure. Addition of benzene (30 c.c.) caused separation of crystals (3·4 g.), which were collected and recrystallised twice from benzene, giving *2-benzyl-DL-4-2′-carboxyethyloxazol-5-one* as colourless needles, m. p. 114—115° (Found: C, 63·2; H, 5·4. $C_{13}H_{13}O_4N$ requires C, 63·1; H, 5·3%). This compound, when exposed to the air, undergoes change over a period of several days and the m. p. drops. Hydrolysis with cold aqueous sodium hydrogen carbonate gave *N*-phenylacetyl-DL-glutamic acid which separated from water in colourless crystals, m. p. 124—125°, having zero rotation. When mixed with *N*-phenylacetyl-L-glutamic acid it softened at 118° and melted between 123° and 125°.

α-Amide (V) *of N-Phenylacetyl-DL-glutamic Acid.*—The oxazolone (IV) (0·5 g.), dissolved in chloroform (15 c.c.), was treated with dry ammonia, a sticky mass being precipitated. After 12 hours the mixture was shaken with water (10 c.c.), and the aqueous layer acidified and extracted with ethyl acetate. The residue (0·34 g.) left after drying and removal of the solvent was crystallised 3 times from acetone–light petroleum (b. p. 60—80°), and the *amide* was obtained as needles, m. p. **144—146°** (Found: C, 59·2; H, 6·0; N, 10·8. $C_{13}H_{16}O_4N_2$ requires C, 59·2; H, 6·1; N, 10·6%).

α-Hydrazide (VI) *of N-Phenylacetyl-DL-glutamic Acid.*—(a) *From the α-methyl ester of N-phenylacetyl-DL-glutamic acid.* The oxazolone (IV) (0·5 g.) was dissolved in anhydrous methanol and, after 12 hours, removal of the excess of alcohol gave an oil. This was dissolved in methanol (5 c.c.) and treated with 96% hydrazine hydrate (0·27 c.c.). After 24 hours the solution was rendered just acid to methyl-orange; and the hydrazide (VI) (0·23 g.) gradually separated. It crystallised from water in small needles, m. p. 181° (decomp.) (Found: C, 56·7; H, 6·3; N, 14·0. Calc. for $C_{13}H_{17}O_4N_3$: C, 55·9; H, 6·1; N, 15·0%).

(b) *From the oxazolone* (IV). The oxazolone (18·3 g.) was dissolved in 96% hydrazine hydrate (28 c.c.), then acidified to methyl-orange after 12 hours, and the solid collected and recrystallised from water, giving the hydrazide, m. p. 181° (11·8 g.).

The iso*propylidene* derivative of the hydrazide (VI) was prepared by dissolving the hydrazide (100 mg.) in acetone (3 c.c.), the crystals (74 mg.) being collected after 24 hours. It separated from light petroleum (b. p. 60—80°)–ethanol in compact crystals, m. p. 161—162° (Found: C, 60·2; H, 6·8. $C_{16}H_{21}O_4N_3$ requires C, 60·1; H, 6·6%). The *benzylidene* derivative of the hydrazide (VI) was prepared by shaking a solution of the hydrazide (200 mg.) in 0·5N-hydrochloric acid (5 c.c.) with benzaldehyde (0·11 c.c., 1·5 mols.), immediate separation of a precipitate occurring (260 mg.). The subtance separates from alcohol in microscopic crystals, m. p. 213—214° (Found: C, 65·2; H, 5·8. $C_{20}H_{21}O_4N_3$ requires C, 65·4; H, 5·7%).

Condensation of the α-Azide of N-Phenylacetyl-DL-glutamic Acid with D-Penicillamine. N-(*N-Phenylacetyl-α-DL-glutamyl*)-D-*penicillamine* (I; R = H).—To an ice-cooled, stirred solution of the hydrazide (VI) (1·6 g.) in 0·5N-hydrochloric acid (11·5 c.c.) was slowly added sodium nitrite (1·3 g., 1·2 mols.). After 15 minutes a slight excess (1·5 mols.) of potassium carbonate and a solution of D-penicillamine hydrochloride (1·7 g.) in dilute aqueous potassium carbonate (1 equiv.) were added, and the mixture was stirred for 45 minutes and then acidified with 2N-hydrochloric acid. The liberated oil was extracted into ethyl acetate, the extract washed and dried, the solvent evaporated at a low temperature, and the product finally dried in a vacuum, leaving a light, brittle mass (1·21 g.) (Found: C, 56·2; H, 6·2; N, 6·3. Calc. for $C_{18}H_{24}O_6N_2S$: C, 54·5; H, 6·1; N, 7·1%). With aqueous ferric chloride the compound gives a blue colour which rapidly fades.

Methyl Ester of α-Hydrazide of N-Phenylacetyl-DL-glutamic Acid.—The hydrazide (VI) (1 g.) in methanol (50 c.c.) was treated with an excess of ethereal diazomethane at 0°. After evolution of nitrogen had ceased, the solvents were removed under diminished pressure at room temperature, the residue was treated with a few c.c. of ether, and the solid collected (0·94 g.). This hydrazide was characterised by its condensation products with acetone and benzaldehyde, which were prepared as in the case of the

hydrazide (VI). The isopropylidene derivative separated from light petroleum (b. p. 60—80°)–acetone in compact crystals, m. p. 149° (Found: C, 61·3; H, 7·1. $C_{17}H_{22}O_4N_2$ requires C, 61·2; H, 6·9%). The benzylidene derivative separated from 50% ethanol as a microcrystalline powder, m. p. 176° (Found: C, 65·8; H, 6·2. $C_{21}H_{22}O_4N_2$ requires C, 66·1; H, 6·0%).

The methylated hydrazide was further converted into the azide which was allowed to react with D-penicillamine methyl ester in ethyl acetate solution. Condensation undoubtedly took place, but the product could not be obtained crystalline.

Condensation of the Oxazolone (IV) *with* D-*Penicillamine Methyl Ester. Methyl Ester of* N-(N-*Phenylacetyl*-α-DL-*glutamyl*)-D-*penicillamine* (I; R = Me).—A solution of free D-penicillamine methyl ester in chloroform prepared from the hydrochloride (0·3 g.) was added to a solution of the oxazolone (IV) (0·3 g.) in chloroform. Next morning the chloroform solution was well washed with dilute acid, then dried, and the solvent removed *in vacuo*, leaving an oil which set to a brittle glass which could not be crystallised (0·38 g.) (Found: C, 55·0; H, 6·7; S, 7·7. $C_{19}H_{24}O_6N_2S$ requires C, 55·6; H, 6·3; N, 6·8; S, 7·8%). The product gave no colour with ferric chloride.

Hydrolysis of this *methyl* ester of *N*-(*N*-phenylacetyl-α-DL-glutamyl)-D-penicillamine (40 mg.) was effected with N-sodium hydroxide (0·5 c.c.; 5 mols.) for ½ hour on the water-bath. After acidification and extraction with ethyl acetate, *N*-phenylacetyl-α-DL-glutamyl-D-penicillamine was obtained as a non-crystalline glass which gave a transient blue colour with aqueous ferric chloride (Found: equiv., 200. Calc. for $C_{18}H_{24}O_6N_2S$: equiv. as a dibasic acid, 198).

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256. ω-Halogenomethyl-pyridines, -quinolines, and -isoquinolines. Part I. Preparation.

By B. R. BROWN, D. LL. HAMMICK, and B. H. THEWLIS.

In order to extend the availability of ω-mono-, -di-, and -tri-halogeno-derivatives of methyl-pyridines, -quinolines, and -*iso*quinolines, ω-chlorination and bromination in acetic acid–sodium acetate mixtures (cf. Koenigs, *Ber.*, 1898, **31**, 2364; Hammick, *J.*, 1923, **123**, 2882; 1926, 1302) has been carried out in a number of new instances (*e.g.*, γ-picoline, 2 : 4-dimethylquinoline, and *N*-methyl-lepidinium iodide). ω-Monohalogeno-derivatives of 3-methylquinoline, lepidine, 1-methyl*iso*quinoline, and 3-methyl*iso*quinoline have been prepared from the corresponding alcohols. Improved methods for the reduction of the ωωω-trihalogeno-compounds to di- and mono-derivatives have been worked out, and the use of the monohalogeno-derivatives illustrated in typical reactions with Grignard reagents, acetoacetic ester, and malonic ester.

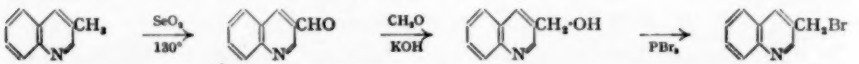
THERE is apparently no recorded example of chlorination or bromination in the side chain of methyl-pyridines, -quinolines, and -*iso*quinolines by the standard procedures (free halogen in carbon disulphide or acetic acid, etc.). Koenigs (*Ber.*, 1898, **31**, 2364) succeeded, however, in producing ωωω-tribromo-8-nitrolepidine by the action of bromine in acetic acid containing sodium acetate; attempts to obtain ωωω-tribromolepidine by this procedure failed. Subsequently the ω-chlorination and bromination of quinaldine, the ω-chlorination of α-picoline (it has not been found possible to bring about direct ω-bromination of the picolines), the ω-bromination of 5- and 8-nitro-quinaldine and of 2-methylquinoxaline and 9-methylphenanthridine, and the bromination of the 2-methyl group in 2 : 3-dimethyl- and 2 : 6-dimethyl-quinoline were accomplished in acetic acid containing sodium acetate (Hammick, *J.*, 1923, **123**, 2882; 1926, 1302; Dyson and Hammick, *J.*, 1939, 781; Bennett and Willis, *J.*, 1928, 1960; Brown, *J.*, 1949, 2577; Brown and Hammick *J.*, 1950, 628). It was suggested (Dyson and Hammick, *loc. cit.*) that the function of the sodium acetate is to "buffer" the reaction by removing halogen acid as it is formed. We shall, however, produce evidence in a later communication that the process involved is most likely a base-catalysed halogenation, the acetate ion being the base.

The ω-tribromination of quinaldine is readily accomplished in acetic acid–sodium acetate mixture in almost quantitative yield (Hammick, *loc. cit.*, 1923); α-picoline is equally easily trichlorinated, but it is necessary to fractionate the product (Dyson and Hammick, *loc. cit.*). In none of these cases is it possible to control the halogenation and to produce mono- and di-halogenated products directly, the obvious inference being that progressive ω-substitution

increases the rate of substitution. Di- and mono-halogeno-derivatives must therefore be obtained by reduction of the trihalogeno-compounds.

The ready availability of ω-mono-, -di-, and -tri-halogeno-derivatives of methyl-pyridines, -quinolines, and -*iso*quinolines is of some importance in that they provide in many cases convenient alternative routes to carbinols, aldehydes, and carboxylic acids. The ω-trihalogeno-compounds are readily hydrolysed by acids; their ω-di- and -mono-analogues are, surprisingly, extremely resistant to hydrolytic agents, but can nevertheless be readily dehalogenated by treatment with alcoholic-aqueous silver nitrate. We therefore report in this paper (i) improved methods for the reduction of ωωω-tribromoquinaldine to di- and monobromoquinaldines, and (ii) the preparation and characteristation of a number of ω-chloro- and ω-bromo-derivatives of γ-picoline, quinaldine, 3-methylquinoline, lepidine, 1-methyl*iso*quinoline, and 3-methyl*iso*quinoline. In addition, we give examples of the reactivity of ω-monobromoquinaldine with acetoacetic and malonic esters. None of the halogenated substances we have examined appears to form a Grignard reagent.

The success of the direct halogenation of methyl side chains in acetic acid–sodium acetate mixtures is dependent on the position of the side chain, and on the structure of the heterocyclic molecule. The exact relationship will be discussed in a later communication on the mechanism of halogenation, but it is now pointed out that direct halogenation is impossible with β-picoline, 3-methylquinoline, lepidine, and 1-, 3-, and 4-methyl*iso*quinolines. Also, it is sometimes possible to achieve direct chlorination when bromination fails, *e.g.*, with α- and γ-picolines. The ω-monobromo-derivatives of 3-methylquinoline, lepidine, 1-methyl*iso*quinoline, and 3-methyl-*iso*quinoline have therefore been prepared from the corresponding alcohols obtained by formaldehyde reduction of the aldehydes, which were prepared by oxidation of the parent methyl compounds with selenium dioxide, *e.g.*:



All six ω-chloro- and ω-bromo-derivatives of quinaldine have now been prepared. A comparison of their solubilities in acids, and of their facility for forming picrates, indicates an increase of basicity with decrease of halogen substitution. The direct iodination of quinaldine has not been achieved, and no ω-iodo-derivatives are yet known.

Experimental.

M. p.s and b. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, and by Mr. F. C. Hall.

ωωω-Trichloro-γ-picoline.—A mixture of γ-picoline (21 ml.), acetic anhydride (20 ml.), sodium acetate (60 g.), and acetic acid (250 ml.) was kept at 80°, and dry chlorine passed in until 3 molecules (50 g.) per molecule of picoline had been absorbed. The mixture was poured on ice and made alkaline with ammonia, and an oil isolated by means of ether. Two fractionations under reduced pressure yielded *ωωω-trichloro-γ-picoline* (15·4 g., 37%) as a colourless oil, b. p. 105—107°/18 mm. (Found: Cl, 54·1. $C_6H_4NCl_3$ requires Cl, 54·2%). The product had a smell reminiscent of that of chloroform, and was insoluble in water (dense lower layer); it decomposed on storage, a black deposit forming in a few days. The *picrate* separated from alcohol as small yellow needles, m. p. 154° (Found: Cl, 24·9. $C_{12}H_7O_7N_4Cl_3$ requires Cl, 25·1%). Hydrolysis of ωωω-trichloro-γ-picoline with silver nitrate in aqueous acetic acid yielded *iso*nicotinic acid (32%) (isolated as its copper salt), which separated from alcohol as colourless needles, m. p. 315°. Spath and Spitzer (*Ber.*, 1926, **59**, 1477) record m. p. 315—316°.

ωω-Dichloro-γ-picoline.—A solution of tin (2·5 g.) in hydrochloric acid (*d* 1·16; 10 ml.) was heated with ωωω-trichloro-γ-picoline (4·0 g.) and acetone (30 ml.) on the water-bath for one hour. Removal of the acetone, steam-distillation, and ether-extraction yielded an oil, which on distillation gave *ωω-dichloro-γ-picoline* (1·6 g., 49%) as a colourless oil of penetrating odour, b. p. 78—80°/18 mm. (Found: Cl, 43·6. $C_6H_5NCl_2$ requires Cl, 43·8%). The substance darkened rapidly on storage. Hydrolysis with silver nitrate yielded *iso*nicotinaldehyde (55%) which formed a picrate, m. p. 168—169°, and a phenylhydrazone, m. p. 177—178°. Wibaut, Kroogman, and Boer (*Rec. Trav. chim.*, 1936, **55**, 293) report similar values.

ωω-Dichloroquinaldine.—ωωω-Trichloroquinaldine (5·0 g.) (Hammick, *J.*, 1923, 2882) in acetic acid (50 ml.) was mixed with a solution of tin (2·5 g.) in hydrochloric acid (*d* 1·16; 8·3 ml.) and boiled under reflux for 1 hour. The mixture was poured into water (500 ml.) and neutralised with chalk, and a solid isolated by ether-extraction. Recrystallisation from aqueous methanol yielded *ωω-dichloroquinaldine* (3·1 g., 72%) as small colourless needles, m. p. 82° (Found: Cl, 33·6. $C_{10}H_7NCl_2$ requires Cl, 33·5%).

ω-Monochloroquinaldine.—ωωω-Trichloroquinaldine (5·0 g.) in acetic acid (50 ml.) was reduced as described above with a solution of tin (5·0 g.) in hydrochloric acid (*d* 1·16; 20 ml.). Crystallisation of the isolated oil from light petroleum (b. p. 40—60°) gave *ω-monochloroquinaldine* as colourless needles, m. p. 54° (Found: Cl, 20·2. $C_{10}H_8NCl$ requires Cl, 20·0%). The substance darkened after a time. The *picrate* separated from alcohol as a microcrystalline powder, m. p. 172° (Found: Cl, 8·9. $C_{16}H_{11}O_7N_4Cl$ requires Cl, 8·7%).

The *picrate* of ωω-dibromoquinaldine (Hammick *J.*, 1926, 1302) separated from alcohol as a yellow microcrystalline powder, m. p. 151° (Found: Br, 30·1. $C_{16}H_{10}O_7N_4Br_2$ requires Br, 30·2%).

ω-Monobromoquinaldine.—The following strictly controlled conditions were essential to success. Granulated tin (6·4 g.) was boiled with hydrobromic acid (*d* 1·51; 40 ml.) until dissolution was complete (1—2 hours). ωωω-Tribromoquinaldine (10·0 g.) was dissolved in acetone (50 ml.) in a 500-ml. flask fitted with a condenser, a stirrer, and a delivery funnel with the stem extending below the surface of the liquid, which was boiled on the water-bath and stirred vigorously. The stannous bromide solution was cooled to 50°, swirled round vigorously, and treated with acetone (50 ml.), whereby the temperature rose to 56°; the hot liquid was at once added to the solution of tribromoquinaldine at such a rate as to keep the very vigorous reaction under control. The mixture was refluxed for 1 hour, and the acetone then removed. Treatment of the residue with ice, exact neutralisation with ammonia, and ether-extraction yielded an oil which crystallised overnight. Crystallisation from light petroleum (b. p. 60—80°) gave *ω-monobromoquinaldine* (3·2 g., 54%) as colourless needles, m. p. 57° (Found: Br, 36·2. $C_{10}H_8NBr$ requires Br, 36·0%). The compound decomposes on storage. Hammick (*J.*, 1926, 1302) records m. p. 83° for "ω-monobromoquinaldine." Repetition of the reduction of ωωω-tribromoquinaldine with stannous chloride (Hammick, *loc. cit.*) yielded ω-monochloroquinaldine, m. p. 54°, an exchange of chlorine for bromine occurring on using stannous chloride as reducing agent. The *picrate* of ω-monobromoquinaldine separated from alcohol as a yellow powder, m. p. 178° (Found: Br, 17·8. $C_{16}H_{11}O_7N_4Br$ requires Br, 17·7%).

N-2-*Quinolylmethylpyridinium Bromide.*—ω-Monobromoquinaldine (1·9 g.), pyridine 10 ml.), and benzene (30 ml.) were boiled for 3 hours. The benzene was decanted, and the deposited solid recrystallised from alcohol to yield N-2-*quinolylmethylpyridinium bromide* (2·4 g., 93%) as colourless needles, m. p. 239° (Found: Br, 26·9. $C_{15}H_{13}N_2Br$ requires Br, 26·6%).

2-*Ethylquinoline.*—The Grignard solution from magnesium (0·49 g.), methyl iodide (1·25 ml.), and ether (50 ml.) was boiled for 1 hour with a solution of ω-monobromoquinaldine (4·5 g.) in ether (25 ml.). Decomposition with water and ether-extraction yielded 2-ethylquinoline (2·14 g., 68%) as a colourless oil, b. p. 134—136°/16 mm. (Found: N, 8·7. Calc. for $C_{11}H_{11}N$: N, 8·9%). Delaby and Hiron (*Bull. Soc. chim.*, 1930, **47**, 1395) record b. p. 128—131°/13 mm.

Ethyl α-2-*Quinolylmethylacetoacetate.*—A solution of sodium (0·25 g.) in alcohol (30 ml.) was cooled to 15°. Ethyl acetoacetate (1·2 ml.) was added, followed by ω-monobromoquinaldine (2·3 g.) in alcohol (5 ml.), and the mixture boiled for 2 hours; it was then neutral to litmus. Removal of alcohol, treatment with water, and ether-extraction gave ethyl α-2-quinolylmethylacetoacetate (2·55 g., 91%) as an oil which was not further purified, since it did not crystallise, and distillation caused decomposition. The 2:4-*dinitrophenylhydrazone* separated from alcohol as orange needles, m. p. 140° (Found: C, 58·9; H, 4·5; N, 15·7. $C_{22}H_{21}O_6N_5$ requires C, 58·5; H, 4·6; N, 15·5%).

Acid hydrolysis: β-2-*quinolylpropionic acid.* Hydrolysis of the foregoing ester with 5% alcoholic potash yielded β-2-quinolylpropionic acid (67%), which separated from benzene as colourless crystals, m. p. 120—121°. Koenigs (*Ber.*, 1900, **33**, 220) records m. p. 122—123°.

Ketonic hydrolysis: *methyl* β-2-*quinolylethyl ketone.* Ethyl α-2-quinolylmethylacetoacetate (0·5 g.) and water (10 ml.) were kept at 200° in a sealed tube for 18 hours. The resulting liquid was made acid with hydrochloric acid, boiled with charcoal, and filtered, and the filtrate made slightly alkaline with aqueous ammonia. Ether-extraction gave methyl β-2-quinolylethyl ketone (0·25 g., 70%) as an oil which was not purified further. The 2:4-*dinitrophenylhydrazone* separated from alcohol as small orange-coloured needles, m. p. 196° (Found: C, 59·9; H, 4·5; N, 18·1. $C_{19}H_{17}O_4N_5$ requires C, 60·1; H, 4·6; N, 18·5%).

Diamide of 2-*Quinolylmethylmalonic Acid.*—A solution of sodium (0·25 g.) in alcohol (30 ml.) was treated at 15° with ethyl malonate (1·5 ml.) and ω-monobromoquinaldine (2·3 g.) in alcohol (5 ml.). The mixture was boiled for 2 hours, the alcohol removed, and the residue treated with water and extracted with ether to yield ethyl 2-quinolylmethylmalonate (0·28 g., 90%) as a yellowish oil which was not further purified. After 4 days with excess of aqueous ammonia and sufficient alcohol to produce a homogeneous solution it gave the *diamide*, which separated from aqueous alcohol as colourless plates, m. p. 245° (decomp.) (Found: C, 64·3; H, 5·3; N, 16·6. $C_{15}H_{15}O_2N_5$ requires C, 64·1; H, 5·3; N, 17·2%).

1:2-*Di*-2′-*quinolylethane.*—ω-Monobromoquinaldine (2·2 g.) in xylene (50 ml.) was treated with sodium wire (2·0 g.) and heated under reflux in an oil-bath for 6 hours. The xylene was decanted and evaporated off under reduced pressure. The residue was taken up in light petroleum (b. p. 60—80°) from which 1:2-*di*-2′-*quinolylethane* (0·65 g., 46%) was deposited as light orange needles, m. p. 160° (Found: N, 9·4. $C_{20}H_{16}N_2$ requires N, 9·8%). The *dipicrate* separated from alcohol as fine yellow needles, m. p. 177° (Found: N, 14·9. $C_{32}H_{22}O_{14}N_8$ requires N, 15·1%).

2-*Quinolylmethyl Quinaldinate.*—A mixture of ω-monobromoquinaldine (1·0 g.) in alcohol (15 ml.) with a solution of quinaldinic acid (1·0 g.) in 2N-sodium carbonate (5 ml.) was refluxed for 3 hours. In the cold the *ester* separated as small pale yellow needles (0·8 g., 57%). Two recrystallisations from alcohol yielded slender colourless needles, m. p. 185—186° (Found: C, 76·6; H, 4·6. $C_{20}H_{14}O_2N_2$ requires C, 76·4; H, 4·45%).

Quinoline-3-*aldehyde.*—3-Methylquinoline (4·0 g.) and freshly prepared and sublimed selenium dioxide (3·4 g.) were heated over a low flame. At about 130° a violent reaction occurred, the temperature rising to 200°. When the reaction had slackened, the mixture was kept at 260—270° for 10 minutes to distil out unchanged 3-methylquinoline. The cold mixture was extracted with ether, the ether removed from the extract, and the residue crystallised from water. Quinoline-3-aldehyde (1·8 g., 41%) formed colourless needles, m. p. 69·5° (Found: N, 8·8. Calc. for $C_{10}H_7ON$: N, 8·9%). Cook, Heilbron, and Steger (*J.*, 1943, 415) record m. p. 70°.

3-*Quinolylmethanol* (3-*Hydroxymethylquinoline*).—A mixture of quinoline-3-aldehyde (1·8 g.), 40% formaldehyde solution (2·9 ml.), potassium hydroxide (2·0 g.), and water (7·5 ml.) was shaken for 3 hours. It was then extracted with chloroform, and the extract washed with sodium hydrogen sulphite solution, sodium carbonate solution, and finally with water. Evaporation yielded a solid residue which crystallised from benzene to yield the *alcohol* (1·5 g., 79%), m. p. 65—67° (Found: C, 75·7; H, 5·5; N, 8·6. $C_{10}H_9ON$ requires C, 75·5; H, 5·7; N, 8·9%).

3-*Bromomethylquinoline*.—3-Quinolylmethanol (2·0 g.) in benzene (20 ml.) was cooled in ice and treated with phosphorus tribromide (1·0 ml.) in benzene (10 ml.). The hydrobromide of the product separated as a yellow solid. The mixture was treated with aqueous ammonia until alkaline, and the precipitate was decomposed, and the product passed into the benzene layer. This was separated, washed, dried, and evaporated. The residue was extracted with light petroleum (b. p. 60—80°) to give 3-*bromomethylquinoline* (2·0 g., 72%) as small needles, m. p. 54·5° (Found: C, 54·2; H, 3·4; Br, 36·7. $C_{10}H_8NBr$ requires C, 54·1; H, 3·6; Br, 36·0%).

2 : 4-*Dinitrophenylhydrazone of Quinoline-4-aldehyde* (Kaplan, *J. Amer. Chem. Soc.*, 1941, **63**, 2654; Kwartler and Lindwall, *ibid.*, 1937, **59**, 524).—The *compound* separated from aqueous pyridine as brick-red crystals, m. p. 258° (Found: C, 57·2; H, 3·9; N, 20·0. $C_{16}H_{11}O_4N_5$ requires C, 57·0; H, 3·3; N, 20·7%).

4-*Quinolylmethanol* (4-*Hydroxymethylquinoline*).—A mixture of quinoline-4-aldehyde (1·8 g.), 40% formaldehyde solution (2·9 ml.), water (7·5 ml.), and potassium hydroxide (2·0 g.) was shaken for 3 hours. The oil which separated crystallised overnight. Recrystallisation from benzene yielded the alcohol (1·6 g., 87%), m. p. 97—98° (Found: N, 8·8. Calc. for $C_{10}H_9ON$: N, 8·9%). Phillips (*J. Amer. Chem. Soc.*, 1946, **68**, 2568) and MacDonald (*ibid.*, 1947, **69**, 1219) record m. p. 99—100° and 96—97°, respectively.

ω-Monobromolepidine.—This was obtained by the method used for 3-bromomethylquinoline. 4-Quinolylmethanol (2·0 g.) yielded *ω-monobromolepidine* (2·1 g., 75%), which separated from light petroleum (b. p. 60—80°) as small plates, m. p. 65° (Found: C, 53·7; H, 4·0; Br, 36·0. $C_{10}H_8NBr$ requires C, 54·1; H, 3·7; Br, 36·0%). The *picrate* separated from alcohol as yellow crystals, m.p. 192° (Found: C, 43·6; H, 2·5; Br, 17·7. $C_{16}H_{11}O_7N_4Br$ requires C, 43·1; H, 2·5; Br, 17·7%).

N-4-*Quinolylmethylpyridinium Bromide*.—ω-Monobromolepidine (1·5 g.), pyridine (10 ml.), and benzene (30 ml.) were refluxed for 3 hours. The solid product which separated crystallised from alcohol to yield N-4-*quinolylmethylpyridinium bromide* (1·9 g., 92%) as colourless needles, m. p. 217° (Found: C, 59·3; H, 4·7; Br, 26·6. $C_{15}H_{13}N_2Br$ requires C, 59·8; H, 4·3; Br, 26·6%).

1 : 2-*Di-4'-quinolylethane*.—This compound was prepared from ω-monobromolepidine (2·0 g.) by the method described above for the preparation of the 2'-isomer. 1 : 2-*Di-4'-quinolylethane* (0·53 g., 42%) separated from light petroleum (b. p. 60—80°) as colourless plates, m. p. 182° (Found: C, 83·9; H, 5·5; N, 9·85. $C_{20}H_{16}N_2$ requires C, 84·5; H, 5·6; N, 9·85%).

ωωω-Tribromo-N-methyl-lepidinium Bromide.—A solution of methyl-lepidinium iodide (5·7 g.) (Hoogewerff and Van Dorp, *Rec. Trav. chim.*, 1883, **2**, 318) and sodium acetate (20 g.) in water (100 ml.) was stirred and kept at 80—90° while bromine (7·0 ml.) was slowly added. The iodine at first precipitated gradually disappeared and a dark oil separated. Eventually the aqueous layer became clear. The mixture was stirred for a further ½ hour and allowed to cool, the aqueous layer decanted, and the semi-solid residue crystallised several times from alcohol. The *bromide* (5·8 g., 61%) separated as dark orange needles, m. p. 159° (Found: Br, 67·1. $C_{11}H_9NBr_4$ requires Br, 67·4%).

Hydrolysis. *ωωω*-Tribromo-*N*-methyl-lepidinium bromide (5·0 g.) in acetic acid (50 ml.) was treated with a solution of silver nitrate (9·0 g.) in water (20 ml.), and the mixture heated on the water-bath for 2 hours. It was then treated with excess of hydrochloric acid and filtered, and the filtrate diluted and made just alkaline with ammonia. The resulting white precipitate crystallised from alcohol to yield 2-hydroxy-*N*-methylcinchoninic acid (1·3 g., 62%) as colourless needles, m. p. 249°, unchanged on admixture with an authentic specimen.

4-*Methyl-2-tribromomethylquinoline*.—Bromination of 2 : 4-dimethylquinoline (2·5 g.) (Vaughan, *Org. Synth.*, 1948, **28**, 49) by Hammick's method (*J.*, 1923, **123**, 2882) yielded 4-*methyl-2-tribromomethylquinoline* (5·2 g., 78%), which separated from alcohol as colourless needles, m. p. 162° (Found: Br, 60·9. $C_{11}H_8NBr_3$ requires Br, 60·9%). Hydrolysis with aqueous-alcoholic silver nitrate yielded 4-methylquinoline-2-carboxylic acid (62%), which separated from light petroleum (b. p. 80—100°) as small slightly yellow needles, m. p. 153°. Koenigs and Mengel (*Ber.*, 1904, **37**, 1327) record m. p. 153—154°.

1-iso*Quinolylmethanol* (1-*Hydroxymethylisoquinoline*).—*iso*Quinoline-1-aldehyde (1·8 g.) (Barrows and Lindwall, *J. Amer. Chem. Soc.*, 1942, **64**, 2430) was reduced to the carbinol by the method used for 3-quinolylmethanol. 1-iso*Quinolylmethanol* (1·3 g., 69%) formed crystals, m. p. 65°, from benzene (Found: C, 75·5; H, 5·8; N, 8·6. $C_{10}H_9ON$ requires C, 75·5; H, 5·7; N, 8·9%).

1-*Bromomethylisoquinoline*.—The method used for 3-bromomethylquinoline was employed. 1-*iso*-Quinolylmethanol (2·0 g.) yielded 1-*bromomethylisoquinoline* (1·95 g., 70%), which formed small needles, m. p. 56°, from light petroleum (Found: C, 54·4; H, 3·85. $C_{10}H_8NBr$ requires C, 54·1; H, 3·6%).

iso*Quinoline-3-aldehyde*.—3-Methylisoquinoline (20 g.) and freshly prepared and sublimed selenium dioxide (17 g.) were heated over a low flame. At 140° a violent reaction occurred, the temperature rising to 230°. When this had slackened, the mixture was kept at 250° for 10 minutes. Distillation yielded a fraction distilling at 140—180°/25 mm.; redistillation gave an oil, b. p. 165—175°/25 mm., which solidified on cooling. Recrystallisation from light petroleum (b. p. 60—80°) yielded iso*quinoline-3-aldehyde* (8·1 g., 37%) as small colourless needles, m. p. 39—40° (Found: N, 8·8. $C_{10}H_7ON$ requires

N, 8·9%). The 2 : 4-*dinitrophenylhydrazone* separated from pyridine as small flocculent, orange needles, m. p. 276° (Found : C, 57·2; H, 3·5. $C_{18}H_{11}O_4N_5$ requires C, 57·0; H, 3·3%).

3-iso*Quinolylmethanol* (3-*Hydroxymethylisoquinoline*).—*iso*Quinoline-3-aldehyde (5·0 g.) was reduced to the carbinol by the method used for 3-quinolylmethanol. 3-*iso*Quinolylmethanol (3·9 g., 77%) separated from benzene–light petroleum as crystals, m. p. 81°. Erlenmeyer, Baumann, and Serkin (*Helv. Chim. Acta*, 1948, **31**, 1988) record m. p. 81°.

3-*Bromomethylisoquinoline*.—The method used for 3-bromomethylquinoline was employed. 3-*iso*Quinolylmethanol (3·0 g.) yielded 3-bromomethyl*iso*quinoline (2·8 g., 67%) as small needles, m. p. 103·5°, from alcohol. Erlenmeyer *et al.* (*loc. cit.*) record m. p. 103·5°.

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257. *ω-Halogenomethyl-pyridines, -quinolines, and -isoquinolines. Part II. Free-radical Reactions of ω-Halogenomethylquinolines.*

By B. R. BROWN, J. O. GRICE, D. LL. HAMMICK, and B. H. THEWLIS.

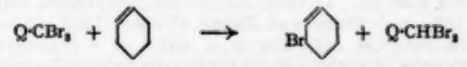
The indication that ωωω-tribromoquinaldine can undergo a free-radical dissociation (Waters and Robertson, *J.*, 1947, 492), $Q{\cdot}CBr_3 \rightleftharpoons Q{\cdot}CBr_2{\cdot} + Br{\cdot}$, has been confirmed by the observance of typical free-radical reactions with the side chains of substituted aromatic hydrocarbons, and of allylic substitution of *cyclo*hexene. ωω-Dibromoquinaldine undergoes these reactions at a higher temperature.

WATERS and ROBERTSON (*J.*, 1947, 492) suggested that "positive" halogen compounds react by way of a homolytic fission of the X–Hal bond. Their evidence is that such compounds (*e.g.*, *N*-bromosuccinimide and bromo-ketones) catalyse the autoxidation of tetralin, which is known to occur by way of a free-radical chain reaction. These workers found that ωωω-tribromoquinaldine catalyses the autoxidation, indicating that it is capable of undergoing a homolytic fission into free radicals. Further evidence for the participation of free radicals in the reactions of ωω-dibromo- and ωωω-tribromo-quinaldine is now presented.

ωωω-Tribromoquinaldine reacts with tetralin at 100° to yield ωω-dibromoquinaldine in 90% yield (Brown and Hammick, *J.*, 1950, 628). Similar reactions occur with xylene and with mesitylene, and it has been shown that about 70% of the bromine lost from the tribromo-compound appears in the aliphatic side chain of the hydrocarbon. This can only be interpreted as a free-radical reaction of the following type :

$$\begin{aligned} Q{\cdot}CBr_3 &\rightleftharpoons Q{\cdot}CBr_2{\cdot} + Br{\cdot} \\ R{\cdot}CH_3 + Br{\cdot} &\longrightarrow R{\cdot}CH_2{\cdot} + HBr \\ R{\cdot}CH_2{\cdot} + Q{\cdot}CBr_3 &\longrightarrow R{\cdot}CH_2Br + Q{\cdot}CBr_2{\cdot} \\ R{\cdot}CH_3 + Q{\cdot}CBr_2{\cdot} &\longrightarrow R{\cdot}CH_2{\cdot} + Q{\cdot}CHBr_2, \text{ etc.} \end{aligned}$$

The second of these reactions is preferred to $R{\cdot}CH_3 + Br{\cdot} \rightarrow R{\cdot}CH_2Br + H{\cdot}$ because free halogen atoms usually react with hydrocarbons by the abstraction of hydrogen and formation of a free hydrocarbon radical (Lu and Sugden, *J.*, 1939, 1273; Brown, Kharasch, and Chao, *J. Amer. Chem. Soc.*, 1940, **62**, 3435). Moreover, ωωω-tribromoquinaldine attacks the allylic position of *cyclo*hexene as does *N*-bromosuccinimide (Ziegler, Spath, Schaaf, Schumann, and Winkelmann, *Annalen*, 1942, **551**, 80) :



This is a typical free-radical reaction (Waters, *J.*, 1937, 2207; *Nature*, 1944, **154**, 772; Schmid and Karrer, *Helv. Chim. Acta*, 1946, **29**, 573). A similar mechanism is applicable to the disproportionation which occurs between ωωω-tribromoquinaldine and ω-monobromoquinaldine at 100° yielding ωω-dibromoquinaldine :

$$\begin{aligned} Q{\cdot}CBr_3 &\rightleftharpoons Q{\cdot}CBr_2{\cdot} + Br{\cdot} \\ Q{\cdot}CH_2Br + Br{\cdot} &\longrightarrow Q{\cdot}CHBr{\cdot} + HBr \\ Q{\cdot}CHBr{\cdot} + Q{\cdot}CBr_3 &\longrightarrow Q{\cdot}CHBr_2 + Q{\cdot}CBr_2{\cdot} \\ Q{\cdot}CH_2Br + Q{\cdot}CBr_2{\cdot} &\longrightarrow Q{\cdot}CHBr_2 + Q{\cdot}CHBr{\cdot}, \text{ etc.} \end{aligned}$$

At a temperature of 140° ωω-dibromoquinaldine undergoes similar reactions. Thus with tetralin, ω-monobromoquinaldine is formed, and a disproportionation between ωω-dibromoquinaldine and quinaldine yields ω-monobromoquinaldine. On account of the decreased crowding of the bromine atoms in ωω-dibromoquinaldine compared with ωωω-tribromoquinaldine, it is to be expected that a higher temperature will be necessary to cause appreciable free-radical dissociation: $Q{\cdot}CHBr_2 \rightleftharpoons Q{\cdot}CHBr\bullet + Br\bullet$.

EXPERIMENTAL.

Reaction of ωωω-Tribromoquinaldine with m-*Xylene and Mesitylene.*—A mixture of ωωω-tribromoquinaldine (10·0 g.) and *m*-xylene or mesitylene (200 ml.) was boiled under reflux for 2 hours. Steam-distillation from dilute (25% by vol.) sulphuric acid (to hold back the ωω-dibromoquinaldine) yielded a mixture of brominated *m*-xylenes and unchanged xylene, which were separated from the aqueous distillate and shaken with aqueous-alcoholic (50% by vol.) silver nitrate for 2 hours. The precipitated silver bromide was separated, washed with water and alcohol, dried at 120°, and weighed. With *m*-xylene, the average of eight runs for the percentage of side-chain bromination was 69; with mesitylene, the average was 75%.

Steam-distillation from alkaline solution after removal of the xylenes yielded ωω-dibromoquinaldine, m. p. and mixed m. p. 119°.

Reaction of ωωω-Tribromoquinaldine with cyclo*Hexene.*—*cyclo*Hexene (80 ml.) and ωωω-tribromoquinaldine (15 g.) were boiled under reflux until a test portion gave no reaction with acidified potassium iodide solution (3 hours). Distillation under reduced pressure gave a solid residue which on crystallisation from light petroleum yielded ωω-dibromoquinaldine (9·2 g., 78%), m. p. and mixed m. p. 119°. The distillate was fractionated to give 1-bromo*cyclo*hex-2-ene (3·8 g., 61%), b. p. 80—82°/40 mm. Ziegler *et al.* (*loc. cit.*) record b. p. 66—68°/35 mm.

Reaction of ωωω-Tribromoquinaldine with ω-Monobromoquinaldine.—ωωω-Tribromo- (1·9 g.) and ω-monobromo-quinaldine (1·1 g.) were heated at 100° for 1 hour. The melt was allowed to cool, and crystallised from light petroleum (b. p. 60—80°) to give ωω-dibromoquinaldine (1·25 g., 42%), m. p. and mixed m. p. 119°.

Thermolysis of ωω-Dibromoquinaldine in Tetralin.—ωω-Dibromoquinaldine (2·5 g.) was dissolved in redistilled tetralin (15 ml.), and heated at 145—150° for 2 hours. The liquid was cooled and shaken with dilute hydrochloric acid. The aqueous extract was shaken with chloroform (to remove traces of tetralin), made alkaline, and extracted with ether. Evaporation of the ether yielded a residue which was crystallised from light petroleum (b. p. 60—80°) to give ω-monobromoquinaldine (1·1 g., 59%) as colourless needles, m. p. and mixed m. p. 56·5°.

Reaction of ωω-Dibromoquinaldine with Quinaldine.—A mixture of ωω-dibromoquinaldine (1·5 g.) and redistilled quinaldine (0·7 ml.) was heated at 145—150° for 2 hours. The mixture was cooled and crystallised from light petroleum (b. p. 60—80°) to give ω-monobromoquinaldine (1·1 g., 50%), m. p. and mixed m. p. 56·5°.

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258. *Synthetic Neuromuscular Blocking Agents. Part I. Heterocyclic Decamethylenebis(quaternary Ammonium Salts).*

By E. P. TAYLOR.

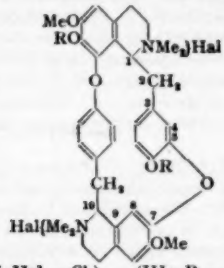
A series of heterocyclic decamethylenebis(quaternary ammonium salts) has been prepared, some of which possess greater curarising activity in rabbits than does (+)-tubocurarine chloride.

IT has long been known that the presence of a quaternary nitrogen atom in a molecule is associated with curarising activity. In 1948, Barlow and Ing (*Nature*, 1948, **161**, 718: *Brit. J. Pharmacol.*, 1948, **3**, 298), and Paton and Zaimis (*Nature*, 1948, **161**, 718), independently investigated the pharmacological activities of a series of polymethylene-αω-bistrimethylammonium salts. Both pairs of workers found the maximum neuromuscular blocking activity to be shown by decamethylenebis(trimethylammonium iodide), now known as decamethonium iodide or C. 10.

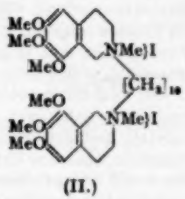
Since the molecule of (+)-tubocurarine chloride (I) also possesses two quaternary nitrogen atoms separated by a chain of ten atoms, it was decided to investigate the effect of maintaining the chain-length at ten, but altering the nature of the terminal quaternary nitrogen groups.

The relation between "curariform" activity and chemical structure has been fully reviewed by Craig (*Chem. Reviews*, 1948, **42**, 285) who states, *inter alia*, that "in general, all of the really effective curare-like compounds have the nitrogen present in a saturated ring," and "the methoxyl group enhances curare action."

The pharmacological properties of the present series of compounds were determined by Dr. H. O. J. Collier, and most have already been briefly reported (Collier and Taylor, *Nature*, 1949, **164**, 491; Taylor and Collier, *ibid.*, 1950, **165**, 602).



(I; R = H, Hal = Cl.) (III; R = Me, Hal = I.)



(II.)

Neostigmine antagonises all of the six compounds of this series which have been examined for this effect in the rabbit. Furthermore, the two most active compounds have been administered to chicks, producing the flaccid paralysis typical of true curariform activity (Buttle and Zaimis, *J. Pharm. Pharmacol.*, 1949, **1**, 991). It can therefore be concluded that the paralysing action of compounds of this type is curariform. The curarising activites of our compounds in rabbits and mice are indicated in Table I. The last three substances

TABLE I.

Paralysing activity of decamethylenebis(quaternary ammonium salts).

(All values in mg. per kg. of body weight.)

Nature of X in I^- $^+\{X\cdot[CH_2]_{10}\cdot X\}^+$ I^-.	MED (rabbit).	ED. 50 (mouse).
Quinolinium	4·5	0·9
1 : 2 : 3 : 4-Tetrahydro-1-methylquinolinium	0·75	0·9
cis-Decahydro-1-methylquinolinium	0·12	convulsant
trans- ,, ,,	0·1	0·75
trans-1-Ethyldecahydroquinolinium	0·4	—
6-Methoxyquinolinium	*ca.* 4·0	1·3
1 : 2 : 3 : 4-Tetrahydro-6-methoxy-1-methylquinclinium	0·2	1·0
8-Methoxyquinolinium	0·2	0·8
1 : 2 : 3 : 4-Tetrahydro-8-methoxy-1-methylquinolinium	0·1	0·6
8-Ethoxyquinolinium	>0·3	—
8-Ethoxy-1 : 2 : 3 : 4-tetrahydro-1-methylquinolinium	*ca.* 0·1	—
6 : 7-Dimethoxyquinolinium	0·15	0·4
1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-1-methylquinolinium	0·08	0·65
*iso*Quinolinium *	*ca.* 4·0	3·6
1 : 2 : 3 : 4-Tetrahydro-2-methyl*iso*quinolinium	1·5	1·9
cis-Decahydro-2-methyl*iso*quinolinium	<0·5	0·7
1 : 2 : 3 : 4-Tetrahydro-6-methoxy-2-methyl*iso*quinolinium	0·2	0·9
6 : 7-Dimethoxy*iso*quinolinium	>1·0	1·8
1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-2-methyl*iso*quinolinium	0·05	0·35
1 : 2 : 3 : 4-Tetrahydro-6 : 7 : 8-trimethoxy-2-methyl*iso*quinolinium	0·02	0·3
1 : 2 : 3 : 4-Tetrahydro-2-methyl-6 : 7-methylenedioxy*iso*quinolinium	0·25	1·2
1 : 2 : 3 : 4-Tetrahydro-2-methyl-6 : 7-methylenedioxy-8-methoxy*iso*quinolinium	0·12	0·85
4-Methylmorpholinium	—	No paralysis
Pyridinium *	—	1·9
1-Methylpiperidinium	—	2·0
3-Bromopyridinium	8·0	0·5
3-Methoxypyridinium	—	No paralysis at 5·0
1-Methylpyrrolidinium	—	1·25 to 1·5
Decamethonium iodide (C. 10)	0·15	0·6
(+)-Tubocurarine chloride	0·1	0·1
(+)-*OO*-Dimethyltubocurarine iodide	0·01	0·12

* Bromide.

are inserted for comparison only. The full pharmacological results will be reported elsewhere by Dr. H. O. J. Collier. It will be observed, however, that, in accordance with the requirements quoted by Craig (*loc. cit.*), reduction of the heterocyclic nucleus, or introduction of methoxyl groups, enhances the curarising activity in the rabbit. The most active of the present series of compounds, decamethylenebis-(1 : 2 : 3 : 4-tetrahydro-6 : 7 : 8-trimethoxy-2-methyl*iso*quinolinium iodide) (II) has each nitrogen atom in a saturated ring and three methoxyl groups in each heterocyclic nucleus. Moreover, it exhibits a close chemical resemblance to (+)-*OO*-dimethyltubocurarine iodide (III). In the rabbit, it is approximately seven times as active as decamethonium iodide, and approximately five times as active as (+)-tubocurarine chloride, and, in this mammal, is one of the most active, purely synthetic, neuromuscular blocking agents yet prepared. It is awaiting clinical trials.

The bisquaternary salts were prepared by two general methods: (i) An excess (usually 50%) of the appropriate tertiary amine was refluxed with a decamethylene dihalide in a neutral solvent (for example, benzene) for, in general, 24—48 hours. The speed and degree of completion of the reaction could be approximately gauged by the rate of precipitation of the required salt. (ii) A 200% excess of an appropriate secondary amine refluxed with a decamethylene dihalide in benzene solution yielded the corresponding bistertiary amine (again, the speed of reaction could be judged by the rate of separation of the hydrohalide of the secondary amine). Treatment of the purified bistertiary amine with an ethereal or benzene solution of an alkyl halide yielded the required bis(quaternary ammonium salt).

However, when 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methylquinoline was refluxed with a benzene solution of decamethylene di-iodide, a very slow reaction occurred, and the resultant quaternary compound, obtained only in a very poor yield, proved to be the methiodide of the original base. In order to obtain decamethylenebis-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methylquinolinium iodide), it was necessary to treat 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxyquinoline first with decamethylene di-iodide, and then with methyl iodide.

Neither 2-methoxypyridine nor 8-methylthioquinoline reacted with decamethylene di-iodide during one month's refluxing. These failures may be due to steric hindrance, since 8-methoxyquinoline reacted with decamethylene di-iodide much more slowly than did the 6-methoxy-compound. Moreover, 8-ethoxyquinoline and decamethylene di-iodide in benzene slowly gave material of vague melting point, probably the monoquaternary compound, 8-ethoxy-1-10′-iododecylquinolinium iodide; if this compound was kept in solution by using alcohol as the solvent instead of benzene, and a further excess of 8-ethoxyquinoline added, the required bisquaternary derivative could be prepared.

Reaction between 6 : 7 : 8-trimethoxyquinoline and decamethylene di-iodide was exceedingly slow, even when alcohol was used. The product, obtained only in very small yield, is as yet unidentified.

6 : 7 : 8-Triethoxy-1 : 2 : 3 : 4-tetrahydro-2-methyl*iso*quinoline reacted very little with decamethylene di-iodide in benzene; in xylene a black oil separated which yielded a very small quantity of 6 : 7 : 8-triethoxy-3 : 4-dihydro-2-methyl*iso*quinolinium iodide.

Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford. All m. p.s and b. p.s are uncorrected.)

I. *Preparation of Simple Heterocyclic Secondary and Tertiary Amines.*—Commercial products, when available, were purified by distillation, recrystallisation, or recrystallisation of derivatives such as the picrates.

Other amines were prepared by the methods described in the literature or as indicated below. For reduction of quinoline and *iso*quinoline derivatives to the tetrahydro-derivatives, sodium and boiling alcohol gave better results than tin and hydrochloric acid (cf. Bamberger and Dieckmann, *Ber.*, 1893, **26**, 1208). The conversion of *N*-alkyl-quinolinium and -*iso*quinolinium halides into the corresponding *N*-alkyltetrahydro-quinolines and -*iso*quinolines was effected by zinc dust and hydrochloric acid, followed by sodium and alcohol, to avoid the possibility of formation of *N*-alkyl dihydro-derivatives.

Quinoline Derivatives.—*cis*- and *trans*-Decahydroquinoline: commercial decahydroquinoline was separated into the *cis*- and *trans*-forms as described by Bailey and McElvain (*J. Amer. Chem. Soc.*, 1930, **52**, 4015).

1 : 2 : 3 : 4-Tetrahydro-6- and -8-methoxy-, and 8-ethoxy-1 : 2 : 3 : 4-tetrahydro-quinoline were obtained by reduction of the corresponding 6- or 8-substituted quinoline derivatives.

6 : 7-Dimethoxyquinoline was prepared by the Skraup reaction from 3 : 4-dimethoxyaniline (Found: C, 69·9; H, 5·8; N, 7·2. Calc. for $C_{11}H_{11}O_2N$: C, 69·8; H, 5·9; N, 7·4%). It has been described by Frisch and Bogert (*J. Org. Chem.*, 1943, **8**, 334) and by Sugasawa, Kakemi, and Tsuda (*Proc. Imp. Acad.*,

Tokyo, 1938, **14**, 67 : *J. Pharm. Soc., Japan*, 1938, **58**, 402), whose data are compared with ours in the following table.

	M. p. or b. p.		
	This paper.	F. and B.	S. *et al.*
Base	33—35°	—	—
	190—191°/11 mm.	164°/2·3 mm.	—
Hydrochloride	233—234 *	222	232° *
Picrate	256	257	251—252 *
Methiodide	271 †	242 *	—
	261 ‡	—	—

* With decomp. † Rapid heating. ‡ Slow heating.

1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxyquinoline, prepared by reduction of the quinoline derivative, crystallised from ether–light petroleum (b. p. 40—60°) as needles, m. p. 43—45°, b. p. 189—191°/9 mm. (Levitz and Bogert, *J. Org. Chem.*, 1945, **10**, 345, give m. p. 45—45·5°). The hydrochloride crystallised from alcohol as needles, m. p. 192—193° (Sugasawa, Kakemi and Tsuda, *loc. cit.*, give m. p. 196°).

1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-1-methylquinoline, obtained by reduction of 6 : 7-dimethoxyquinoline methiodide, formed needles, m. p. 45°, b. p. 174—176°/10 mm., from light petroleum (b. p. 40—60°) (Found : C, 69·6; H, 8·2; N, 6·8. Calc. for $C_{12}H_{17}O_2N$: C, 69·6; H, 8·3; N, 6·8%); its methiodide, prisms (from alcohol), had m. p. 216—217° (Levitz and Bogert, *loc. cit.*, record the base as an oil, b. p. 135—136°/1 mm., and the methiodide as having m. p. 216·5—217·5°).

6 : 7 : 8-*Trimethoxyquinoline*. 2 : 3 : 4-Trimethoxyaniline had b. p. 95—97°/0·1 mm., 154°/13 mm., and its hydrochloride had m. p. 200° (decomp.) (contrast Lions, *J. Proc. Roy. Soc., N.S.W.*, 1929, **63**, 159; Graebe and Suter, *Annalen*, 1905, **340**, 227; Hupe and Schramme, *Z. physiol. Chem.*, 1928, **177**, 317).

The Skraup reaction with 2 : 3 : 4-trimethoxyaniline in nitrobenzene proceeded with almost explosive violence, and it was advisable to use arsenic pentoxide as described by Mietzsch and Klös (U.S.P. 1,790,066) for 6 : 8-dimethoxyquinoline. The resulting 6 : 7 : 8-trimethoxyquinoline melted at 80°, and its picrate at 181°. The *methiodide* separated from ether–alcohol as pale yellow needles, m. p. 139—140° (decomp.) (Found : C, 42·9; H, 4·6; N, 4·0; I, 34·9. $C_{13}H_{16}O_5NI$ requires C, 43·2; H, 4·5; N, 3·9; I, 35·2%).

1 : 2 : 3 : 4-*Tetrahydro*-6 : 7 : 8-*trimethoxyquinoline*, prepared by reduction of the quinoline derivative, had b. p. 139—141°/0·6 mm. (Found : C, 65·0; H, 7·7; N, 6·4. $C_{12}H_{17}O_3N$ requires C, 64·6; H, 7·7; N, 6·3%). The *hydrochloride* crystallised from ether–alcohol as needles, m. p. 206—208° (decomp.) (Found : C, 55·7; H, 7·0; N, 5·2; Cl, 13·5. $C_{12}H_{18}O_3NCl$ requires C, 55·5; H, 7·0; N, 5·4; Cl, 13·7%).

5 : 6 : 7-*Trimethoxyquinoline*. Two attempts to convert 3 : 4 : 5-trimethoxyaniline (Graebe and Suter, *Annalen*, 1905, **340**, 224) into 5 : 6 : 7-trimethoxyquinoline by the Skraup reaction were unsuccessful.

6 : 7-*Methylenedioxyquinoline*, prepared from 3 : 4-methylenedioxyaniline (Rupe and Majewski, *Ber.*, 1900, **33**, 3403) by the Skraup reaction, had b. p. 186—187°/17 mm. and crystallised from light petroleum (b. p. 40—60°) as long needles, m. p. 85° (Found : C, 69·3; H, 4·2; N, 8·05. $C_{10}H_7O_2N$ requires C, 69·4; H, 4·1; N, 8·1%).

8-*Methylthioquinoline*. Quinoline-8-thiol (Edinger, *Ber.*, 1908, **41**, 938) on methylation with methyl iodide and sodium methoxide gave a 70% yield of the crude material, which crystallised from light petroleum (b. p. 40—60°) containing a trace of ether as a cream-coloured powder, m. p. 78—80° (Found : C, 68·1; H, 5·4; N, 7·9; S, 17·8. $C_{10}H_9NS$ requires C, 68·6; H, 5·2; N, 8·0; S, 18·3%).

iso*Quinoline Derivatives*.—1 : 2 : 3 : 4-Tetrahydro-6-methoxy-2-methyl*iso*quinoline gave a picrate as rosettes of needles (from methyl alcohol), m. p. 131—132° (Gulland and Virden, *J.*, 1929, 1798, give 130—131°), and a hydrochloride as prisms (from alcohol–ether), m. p. 170—171° (Buck, *J. Amer. Chem. Soc.*, 1934, **56**, 1771, gives 170°).

6 : 7-*Dimethoxy*iso*quinoline*. Papaverine was oxidized to papaveraldine by selenium dioxide in 92% yield (Taylor, *J. Pharm. Pharmacol.*, 1950, **2**, 324). This, on fusion with potassium hydroxide (Dobson and Perkin, *J.*, 1911, 136), yielded 6 : 7-dimethoxy*iso*quinoline, b. p. 198—200°/10 mm., m. p. 92° [Dobson and Perkin, *ibid.*, p. 137, give m. p. 94·5°; Forsyth, Kelly, and Pyman, *J.*, 1925, 1666, give 93° (corr.); Spath and Polgar, *Monatsh.*, 1929, **51**, 197, give 93—94°]. Its methiodide, needles (from alcohol), had m. p. 237° (decomp.) (Decker and Koch, *Ber.*, 1905, **38**, 1740, give m. p. 236—237°; Forsyth *et al.*, *loc. cit.*, give m. p. 256°).

1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-2-methyl*iso*quinoline, prepared by the reduction of 6 : 7-dimethoxy*iso*quinoline methiodide, crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 82°. The hydrochloride had m. p. 213° and the picrate had m. p. 156—157° (cf. Pyman, *J.*, 1909, 1273; Forsyth, Kelly, and Pyman, *J.*, 1925, 1667; Buck, *J. Amer. Chem. Soc.*, 1934, **56**, 1771).

1 : 2 : 3 : 4-*Tetrahydro*-6 : 7 : 8-*trimethoxy*-2-*methyl*iso*quinoline*.—N-*Formyl*-2-(3 : 4 : 5-*trimethoxyphenyl*)-*ethylamine* (*N-formylmescaline*). Mescaline (Slotta and Heller, *Ber.*, 1930, **63**, 3040; Slotta and Szyszka, *J. pr. Chem.*, 1933, **137**, 345) (25 g.) and formic acid (17·5 g.; 98—100%) were heated under reflux in an oil-bath at 170° for 5 hours and then cooled. Dry benzene (75 ml.) was added and then distilled off during 45 minutes. The residue was distilled *in vacuo*, and the fraction of b. p. 183—184°/0·2 mm. (27 g.) recrystallised from benzene containing a little light petroleum (b. p. 40—60°), giving *N-formyl-*

TABLE II.

Heterocyclic decamethylenebis(tertiary amines).

Secondary base used.	Properties of bis(tertiary amine). M. p.	B. p.	Cryst. form.	Crystn. solvent.	Found, %. C.	H.	N.	Formula.	Required, %. C.	H.	N.
Piperidine	—	154—156°/0·1 mm.	—	—	77·7	12·7	8·9	$C_{20}H_{40}N_2$	77·9	13·1	9·1
Pyrrolidine	—	146—148°/0·5 mm.	—	—	77·1	13·1	10·0	$C_{18}H_{36}N_2$	77·1	13·0	10·0
1 : 2 : 3 : 4-Tetrahydro*iso*quinoline	57—58°	257—260°/0·5 mm.	Needles	aq. EtOH	82·9	9·9	6·6	$C_{28}H_{40}N_2$	83·2	10·0	6·9
Quinolines.											
1 : 2 : 3 : 4-Tetrahydro-	—	235—240°/0·05 mm.	—	—	83·2	10·0	6·8	$C_{28}H_{40}N_2$	83·2	10·0	6·9
trans-Decahydro-	89—90	238—240°/0·2 mm.	Small clusters	aq. EtOH	80·6	12·5	6·7	$C_{28}H_{52}N_2$	80·8	12·6	6·7
cis-Decahydro-	—	234—236°/0·3 mm.	—	—	80·9	12·6	6·6	$C_{28}H_{52}N_2$	80·8	12·6	6·7
1 : 2 : 3 : 4-Tetrahydro-6-methoxy-	74—75	280—285°/0·2 mm.	Plates	EtOH	77·3	9·35	5·9	$C_{30}H_{44}O_2N_2$	77·6	9·6	6·0
1 : 2 : 3 : 4-Tetrahydro-8-methoxy-	67—69	255—260°/0·1 mm.	Needles	aq. EtOH	77·4	9·35	6·0	$C_{30}H_{44}O_2N_2$	77·6	9·6	6·0
8-Ethoxy-1 : 2 : 3 : 4-tetrahydro-	73—74	262—267°/0·2 mm.	Needles	EtOH	77·8	10·0	5·5	$C_{32}H_{48}O_2N_2$	78·0	9·8	5·7
1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-	Not cryst.	Not distilled	—	—	73·6	9·05	5·45	* $C_{32}H_{48}O_4N_2$	73·3	9·2	5·3
" " " picrate	144—145 (decomp.)	—	Powder	EtOH	53·3	5·1	11·4	$C_{44}H_{54}O_{14}N_8$	53·8	5·5	11·4

* The analytical figures are of the undistilled material.

TABLE III.

Heterocyclic decamethylenebis(quaternary ammonium salts).

Nature of X in $I^-{+}\{X{\cdot}[CH_2]_{10}{\cdot}X\}^+I^-$	Method.	M. p. (d = decomp.).	Cryst. form.*	Crystn. solvent.	Found, %.† C.	H.	N.	Hal.	Formula.	Required, %. C.	H.	N.	Hal.
Quinolinium	b	213—214° (d)	Yellow	MeOH–EtOH	51·5	5·15	4·4	39·1	$C_{28}H_{34}N_2I_2$	51·5	5·3	4·3	39·0
1 : 2 : 3 : 4-Tetrahydro-1-methylquinolinium	a	152—153 (d)	Cream	EtOH	52·6	6·75	3·7	36·5	$C_{30}H_{46}N_2I_2$	52·3	6·7	4·1	36·9
cis-Decahydro-1-methylquinolinium	a	235—237 (d)	—	EtOH–Et_2O	51·1	8·3	3·8	36·0	$C_{30}H_{58}N_2I_2$	51·4	8·35	4·0	36·3
trans- " " "	a	234—235 (d) [1]	—	EtOH–Et_2O	51·1	8·35	3·9	35·8	$C_{30}H_{58}N_2I_2$	51·4	8·35	4·0	36·3
trans-1-Ethyldecahydroquinolinium	a [2]	238—239 (d)	—	EtOH–Et_2O	52·6	8·45	3·9	35·1	$C_{32}H_{62}N_2I_2$	52·7	8·6	3·85	34·9
6-Methoxyquinolinium	b	185—186 (d)	Yellow plates	MeOH–EtOH	50·4	5·7	3·9	35·1	$C_{30}H_{38}O_2N_2I_2$	50·6	5·4	3·9	35·7
1 : 2 : 3 : 4-Tetrahydro-6-methoxy-1-methylquinolinium	a	168—169	—	EtOH	51·5	6·8	3·75	33·8	$C_{32}H_{46}O_2N_2I_2$	51·3	6·7	3·7	34·0
8-Methoxyquinolinium	b [3]	178—179 (d)	Yellow	EtOH	50·4	5·4	3·7	35·2	$C_{30}H_{38}O_2N_2I_2$	50·6	5·4	3·9	35·7
1 : 2 : 3 : 4-Tetrahydro-8-methoxy-1-methylquinolinium	a [2]	190—191	—	EtOH–Et_2O	51·3	6·9	3·5	34·0	$C_{32}H_{46}O_2N_2I_2$	51·3	6·7	3·7	34·0

Nature of X in $I^-\{X\cdot[CH_2]_{10}\cdot X\}^+I^-$	Method.	M. p. (d = decomp.).	Cryst. form.*	Crystn. solvent.	Found, %.† C.	H.	N.	Hal.	Formula.	Required, %. C.	H.	N.	Hal.
8-Ethoxyquinolinium	b [3]	182—183 (d)	Yellow plates	EtOH	51·6	6·1	3·9	34·7	$C_{32}H_{42}O_2N_2I_2$	51·9	5·7	3·8	34·3
8-Ethoxy-1 : 2 : 3 : 4-tetrahydro-1-methylquinolinium	a	177—178	—	EtOH–Et_2O	52·3	7·15	3·6	32·5	$C_{34}H_{54}O_2N_2I_2$	52·6	7·0	3·6	32·7
6 : 7-Dimethoxyquinolinium	b	207—209 (d)	Yellow	MeOH–EtOH	49·5	5·5	3·5	32·8	$C_{32}H_{42}O_4N_2I_2$	49·7	5·5	3·6	32·9
1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-1-methylquinolinium	a	209—211	Nodules	EtOH	50·4	6·9	3·5	31·2	$C_{34}H_{54}O_4N_2I_2$	50·5	6·7	3·5	31·4
*iso*Quinolinium [4]	b	Sinters at 135—136°, melts at 171° (d)	Felted mass of small cream needles	EtOH	60·4	6·0	4·8	28·7	$C_{18}H_{24}N_2Br_2$	60·2	6·1	5·0	28·7
*iso*Quinolinium	b	194	Lemon-yellow needles	EtOH	51·5	5·4	4·2	38·6	$C_{18}H_{24}N_2I_2$	51·5	5·3	4·3	39·0
1 : 2 : 3 : 4-Tetrahydro-2-methyl*iso*quinolinium	a	225	—	MeOH–EtOH	52·1	6·5	4·0	37·0	$C_{20}H_{28}N_2I_2$	52·3	6·7	4·1	36·9
cis-Decahydro-2-methyl*iso*quinolinium	b	201—202	—	EtOH	51·2	8·3	3·85	36·2	$C_{20}H_{32}N_2I_2$	51·4	8·35	4·0	36·3
1 : 2 : 3 : 4-Tetrahydro-6-methoxy-2-methyl*iso*quinolinium	b	182—184	—	EtOH	51·2	6·8	3·55	34·1	$C_{22}H_{32}O_2N_2I_2$	51·3	6·7	3·7	34·0
6 : 7-Dimethoxy*iso*quinolinium	b	208—210 (d)	Pale yellow needles	MeOH–EtOH	49·2	5·3	3·7	32·7	$C_{22}H_{32}O_4N_2I_2$	49·7	5·5	3·6	32·9
1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-2-methyl*iso*quinolinium	b	226—228 (d)	Cream	MeOH–EtOH	50·2	6·75	3·3	31·4	$C_{24}H_{36}O_4N_2I_2$	50·5	6·7	3·5	31·4
1 : 2 : 3 : 4-Tetrahydro-6 : 7 : 8-trimethoxy-2-methyl*iso*quinolinium	b	188—190 (d)	Cream nodules	MeOH–EtOH	49·7	6·7	3·0	29·3	$C_{26}H_{44}O_6N_2I_2$	49·8	6·7	3·2	29·3
1: 2 : 3 : 4-Tetrahydro-2-methyl-6 : 7-methylenedioxy*iso*quinolinium	b	222—224	—	MeOH–EtOH	49·6	6·0	3·5	32·6	$C_{22}H_{34}O_4N_2I_2$	49·5	6·0	3·6	32·7
1 : 2 : 3 : 4-Tetrahydro-8-methoxy-2-methyl-6 : 7-methylenedioxy*iso*quinolinium	b	225—227 (d)	—	MeOH–EtOH	48·7	6·0	3·2	30·5	$C_{24}H_{36}O_6N_2I_2$	48·8	6·0	3·35	30·4
1-Methylpiperidinium	a	248 (d)	Needles	EtOH	44·6	7·7	4·7	42·4	$C_{12}H_{26}N_2I_2$	44·6	7·8	4·7	42·9
3-Bromopyridinium	b	173—174	Pale yellow needles [5]	MeOH–EtOH	34·2	4·0	4·05	57·8	$C_{10}H_{10}N_2Br_2I_2$	33·8	4·0	3·9	58·3
3-Methoxypyridinium	b	103—105	Very pale yellow	EtOH	43·3	5·7	4·4	41·1	$C_{12}H_{18}O_2N_2I_2$	43·1	5·6	4·6	41·5
1-Methylpyrrolidinium	a	246—247	Needles	EtOH	42·4	7·5	4·9	45·1	$C_{10}H_{24}N_2I_2$	42·6	7·5	5·0	45·0

* Microcrystalline and colourless unless otherwise stated. † Dried at 100° *in vacuo*.

[1] Mixed m. p. with *cis*-derivative, 218—222°. [2] Reaction slow. [3] Reaction very slow—necessary to use alcohol as solvent instead of benzene. [4] Bromide. Crystals contain $2H_2O$ of crystn. (Hartwell and Pogorelskin, *J. Amer. Chem. Soc.*, 1950, **72**, 2043, give m. p. range of the dihydrate "136 to 180°, giving off vapour at 144—162° "; Barlow and Ing., *Brit. J. Pharmacol.*, 1948, **3**, 298, give m. p. 113°). [5] Crystals contain $2H_2O$ of crystn.

In general, those compounds in which the quaternary nitrogen is present in a reduced ring are colourless or cream-coloured. When the quaternary nitrogen is situated in an unsaturated ring, the resulting iodides are generally yellow or orange, although the bromides are colourless or cream coloured.

mescaline (23 g.) as needles, m. p. 68—69° (Found: C, 60·1; H, 6·95; N, 5·65. $C_{13}H_{17}O_4N$ requires C, 60·25; H, 7·2; N, 5·9%).

3 : 4-*Dihydro*-6 : 7 : 8-*trimethoxy*isoquinoline. *N*-Formylmescaline (23 g.), in a 250-ml. flask fitted with a reflux condenser, was cooled in ice, and phosphorus oxychloride (40 ml.) added through the condenser. When the initial vigorous reaction had subsided, the red solution was heated under reflux on the steam-bath for 90 minutes. After cooling, it was poured into light petroleum (b. p. 40—60°), with stirring, the petroleum decanted off, and the lower layer washed three times by decantation with light petroleum. It was then dissolved in dilute hydrochloric acid, the solution washed once with benzene, made alkaline with sodium hydroxide, and the resulting oil extracted with benzene. The benzene solution was shaken with solid potassium hydroxide and filtered, the benzene recovered, and the residue distilled *in vacuo*. The fraction of b. p. 138—140°/0·5 mm. (16·5 g.) was recrystallised from benzene–light petroleum (b. p. 40—60°). The *product* (15 g.) separated as rhombs, m. p. 91—92° (Found: C, 64·8; H, 6·9; N, 6·2. $C_{12}H_{15}O_3N$ requires C, 65·2; H, 6·8; N, 6·3%).

Its *methiodide*, fine pale yellow needles (from methyl alcohol), had m. p. 179—180° (decomp.) (Found: C, 43·2; H, 4·9; N, 3·8; I, 34·7. $C_{13}H_{18}O_3NI$ requires C, 43·0; H, 5·0; N, 3·9; I, 35·0%). Its *ethiodide*, fine pale yellow needles (from alcohol–ether), had m. p. 155—157° (decomp.) (Found: C, 44·7; H, 5·3; N, 3·8; I, 33·4. $C_{14}H_{20}O_3NI$ requires C, 44·6; H, 5·35; N, 3·7; I, 33·7%).

1 : 2 : 3 : 4-*Tetrahydro*-6 : 7 : 8-*trimethoxy*-2-*methyl*isoquinoline was prepared by reduction of the above methiodide (19 g.) by hydrochloric acid (240 ml. of concentrated acid in 240 ml. of water) and excess of zinc dust. After being made alkaline with excess of ammonia, the cooled solution was extracted with ether in a continuous-extraction apparatus, the ethereal extract dried (Na_2SO_4), the solvent recovered, and the residue distilled *in vacuo*. The *product* (10·5 g.) had b. p. 122—124°/0·5 mm. (Found: C, 65·8; H, 8·0; N, 5·8. $C_{13}H_{19}O_3N$ requires C, 65·8; H, 8·1; N, 5·9%). The *picrate*, thick needles (from alcohol), had m. p. 135° (Found: C, 48·9; H, 4·75; N, 11·6. $C_{19}H_{22}O_{10}N_4$ requires C, 48·9; H, 4·8; N, 12·0%).

2-*Ethyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7 : 8-*trimethoxy*isoquinoline (1·25 g.), obtained by reduction of 3 : 4-dihydro-6 : 7 : 8-trimethoxy*iso*quinoline ethiodide (4·75 g.), had b. p. 107—109/0·05 mm. (Found: C, 66·5; H, 8·6; N, 5·8. $C_{14}H_{21}O_3N$ requires C, 66·9; H, 8·4; N, 5·6%). Its *methiodide*, colourless prisms (from alcohol), had m. p. 171—172° (decomp.) (Found: C, 45·9; H, 5·85; N, 3·45; I, 32·1. $C_{15}H_{24}O_3NI$ requires C, 45·8; H, 6·2; N, 3·6; I, 32·3%).

6 : 7 : 8-*Triethoxy*-1 : 2 : 3 : 4-*tetrahydro*-2-*methyl*isoquinoline was prepared from 2-(3 : 4 : 5-triethoxyphenyl)ethylamine (14 g.) (Slotta and Szyszka, *loc. cit.*, p. 349) in a manner analogous to the preparation of the corresponding trimethoxy-compound from mescaline, *via* the following intermediates: *N*-*formyl*-2-(3 : 4 : 5-*triethoxyphenyl*)*ethylamine* (12 g.), leaflets [from benzene–light petroleum (b. p. 40—60°)], m. p. 67—69°, b. p. 178—180°/0·1 mm. (Found: C, 64·0; H, 8·2; N, 5·0. $C_{15}H_{23}O_4N$ requires C, 64·1; H, 8·25; N, 5·0%); 6 : 7 : 8-*triethoxy*-3 : 4-*dihydro*isoquinoline (9 g.), needles [from light petroleum (b. p. 40—60°)], m. p. 44—46°, b. p. 120—122°/0·1 mm. (Found: C, 68·5; H, 8·0; N, 5·35. $C_{15}H_{21}O_3N$ requires C, 68·4; H, 8·05; N, 5·3%) [*methiodide* (12 g.), pale yellow needles (from alcohol), m. p. 203° (decomp.) (Found: C, 47·2; H, 5·85; N, 3·4; I, 31·5. $C_{16}H_{24}O_3NI$ requires C, 47·4; H, 6·0; N, 3·5; I, 31·4%)]; 6 : 7 : 8-*triethoxy*-1 : 2 : 3 : 4-*tetrahydro*-2-*methyl*isoquinoline, (7 g.), b. p. 127—129°/0·2 mm. (Found: C, 68·5; H, 9·2; N, 4·9. $C_{16}H_{25}O_3N$ requires C, 68·8; H, 9·0; N, 5·0%) [*methiodide*, colourless glistening plates (from alcohol), m. p. 215—216° (Found: C, 48·5; H, 6·7; N, 3·2; I, 30·4. $C_{17}H_{28}O_3NI$ requires C, 48·5; H, 6·7; N, 3·3; I, 30·2%)].

1 : 2 : 3 : 4-Tetrahydro-2-methyl-6 : 7-methylenedioxy*iso*quinoline (hydrohydrastinine), prepared by reduction of 3 : 4-dihydro-6 : 7-methylenedioxy*iso*quinoline methiodide (Spath and Polgar, *Monatsh.*, 1929, **51**, 201; Decker, *Annalen*, 1913, **395**, 324), needles [from light petroleum (b. p. 40—60°)], had m. p. 61° (Fritsch, *Annalen*, 1895, **286**, 18, gives m. p. 60—61°; Freund and Will, *Ber.*, 1877, **20**, 93, give m. p. 66°; Clayson, *J.*, 1949, 2018, gives m. p. 61°).

Pyridine Derivatives.—2-Methoxypyridine, prepared by treatment of the silver derivative of α-pyridone with methyl iodide, had b. p. 144—145° (von Pechmann and Baltzer, *Ber.*, 1891, **24**, 3149, prepared this substance, but did not quote the b. p.) (Found: C, 65·7; H, 6·8; N, 12·7. Calc. for C_6H_7ON: C, 66·1; H, 6·5; N, 12·8%).

3-Methoxypyridine, prepared in a similar manner, had b. p. 182° (Koenigs, Gerdes, and Sirot, *Ber.*, 1928, **61**, 1022, give b. p. 179°).

II. *Preparation of Heterocyclic Decamethylenebis(tertiary Amines).*—These were prepared by refluxing a decamethylene dihalide with an excess of the appropriate heterocyclic secondary amine in benzene. One example is given in detail; the properties of the other bis(tertiary amines) are listed in Table II.

1 : 10-*Dimorpholino*-n-*decane*. Decamethylene dibromide (15 g.) and morpholine (26 g., 6 mols.) in dry benzene (45 ml.) were refluxed on the steam-bath for 24 hours. There was an almost immediate precipitate of morpholine hydrobromide. The mixture was then poured into a slight excess of dilute hydrochloric acid. The benzene layer was separated, washed once with dilute hydrochloric acid, and discarded. The combined aqueous layers were washed with benzene and made alkaline with sodium hydroxide, the resulting oil was extracted with ether, and the ethereal extract washed with water, and dried (Na_2SO_4). After filtration and recovery of the solvent, the residue was distilled *in vacuo*. The fraction, b. p. 162—164°/0·01 mm. (14 g.), of 1 : 10-*dimorpholino*-n-*decane* crystallised in needles, m. p. 48°. Recrystallisation from aqueous alcohol did not alter the m. p. (Found: C, 69·1; H, 11·3; N, 9·0. $C_{18}H_{36}O_2N_2$ requires C, 69·2; H, 11·6; N, 9·0%). The hydrochloride of this base has been described by Goodson *et al.* (*Brit. J. Pharmacol.*, 1948, **3**, 60) as needles, m. p. 240—242°.

III. *Preparation of Heterocyclic Decamethylenebis(quaternary Ammonium) Salts.*—These were obtained by two general methods:

(*a*) By the action of an alkyl halide on an ethereal or benzene solution of a heterocyclic decamethylenebis(tertiary amine), for example: *Decamethylenebis(morpholinium methiodide)*. 1 : 10-Dimorpholino-*n*-decane (10·4 g.) in dry ether (25 ml.) was treated with methyl iodide (14 g., 50% excess) in dry ether (25 ml.). The mixture soon deposited crystals. After 2 days at room temperature, the mixture became almost solid. It was filtered, and the solid washed thoroughly with dry ether, and recrystallised from anhydrous alcohol, giving *decamethylenebis(morpholinium methiodide)* (15 g.) as colourless needles, m. p. 217—218° (decomp.) (Found: C, 40·2; H, 7·05; N, 4·6; I, 42·7. $C_{20}H_{42}O_2N_2I_2$ requires C, 40·3; H, 7·1; N, 4·7; I, 42·6%).

(*b*) By refluxing an excess of the appropriate heterocyclic tertiary amine with a decamethylene dihalide in a neutral solvent, for example: *Decamethylenebis(pyridinium bromide)*. Decamethylene dibromide (10 g.) pyridine (8 g., 3 mols.) in dry benzene (40 ml.) were heated under reflux on the steam-bath for 24 hours. The solution deposited crystals within 15 minutes. After cooling and filtration, the precipitate was washed with dry benzene and recrystallised from anhydrous alcohol, giving *decamethylenebis(pyridinium bromide)* (12 g.) as small hard colourless rhombs, m. p. 194—195 (Found: C, 52·6; H, 6·7; N, 6·0; Br, 34·7. Calc. for $C_{20}H_{36}N_2Br_2$: C, 52·4; H, 6·6; N, 6·1; Br, 34·9%) (Hartwell and Pogorelskin, *J. Amer. Chem. Soc.*, 1950, **72**, 2041, give m. p. 196·5—198°).

The properties of the remaining bis(quaternary ammonium salts) are listed in Table III, the notation (a) or (b) indicating the method of preparation.

I thank Mr. W. C. Austin for technical assistance, Dr. H. O. J. Collier for supplying the pharmacological results, and the Directors of Messrs. Allen and Hanburys Ltd. for permission to publish this work.

RESEARCH DIVISION, ALLEN AND HANBURYS LTD.,
WARE, HERTS.

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259. *Induced and Other Variations in Bacterial Cultures. Part I. The Chemical Basis of the Changes.*

By A. C. R. DEAN and SIR CYRIL HINSHELWOOD.

In order to define the theoretical background for the discussion of ensuing experimental studies, various kinds of chemical basis for variations in bacterial characteristics are classified.

THERE is nothing in the last resort upon which the properties of a bacterial cell can depend except the molecular pattern of its cell substance. This pattern involves (*a*) the structure of individual macromolecules, (*b*) their types of folding, and (*c*) the proportions in which the various sub-patterns are present in the cell as a whole. The existing material is copied with more or less exactness whenever the cell multiplies and divides, the contents being almost equally shared between the two new cells formed.

In principle the essential reproductive parts of the cell may (1) constitute a single whole, more or less equivalent to a uniform phase, or (2) they may separate into mechanically distinguishable units which are virtually separate phases, as appears to happen in cells containing chromosomes. In case (1) the heredity is determined by the direct copying while in (2) it may also be governed largely by redistribution of certain basic structural units when sexual unions are involved.

In both cases the fundamental consideration is the making of replicas of the molecular pattern, but in the second case there is the added variety of recombination or segregation of, as it were, mechanically detachable sub-units of this pattern. The second process is a powerful source of property variations, but can only occur when there are sexual conjugations. With bacteria, such phenomena, although they have been claimed (see review by Lederberg, *Heredity*, 1946, **2**, 145), are at least exceedingly rare and in the vast majority of cases the cells multiply by simple fission without the possibility of recombination phenomena.

The properties of bacterial cells are very much subject to variations. These are sometimes of an adaptive kind, the power to utilise new substrates or to resist inhibitory substances being gradually developed as growth proceeds in suitable media. Other changes in biochemical character are also induced by exposure to ultra-violet light and other radiations or by the action of chemical agencies such as the " nitrogen mustards." Ultra-violet light, in particular, gives rise to mutants which have usually become deficient in certain characters which the cells originally possessed (see, for example, Lea, " Action of Radiations on Living Cells," Cambridge, 1946). Certain biochemical reactions may fail in the mutants, the radiation having evidently destroyed or impaired some part of the molecular structure on which the property depended. These deficient mutants not infrequently recover their lost characteristics when cultivated under conditions which offer the opportunity of exercising the lost or impaired property.

A question of great interest is the chemical basis in general of these various changes, adaptive, mutational, and restitutive. The possible cases of change in general may be classified as follows.

1. Some separable parts of the structure become differently distributed as a result of recombination processes. This with all its subdivisions is essentially the Mendelian hereditary mechanism, which in certain types of phenomenon is of dominant importance. But with bacteria, where on the one hand conjugations are at least very rare (if they occur at all) and on the other hand variability is great, this case does not concern us very much.

2. The structure (including the folding of the macromolecular chains and so on) of a part of the cell may suffer a modification.

3. The *proportions* of different types of structure present in different regions of a cell may suffer *quantitative* modification. (This may be referred to for brevity as a change in enzyme proportions—though " enzyme " is here understood in a rather broad sense.)

Mixed cases of 2 and 3 with 1 would also be possible in suitable organisms.

Both 2 and 3 are subdivided in another way :

A. The change occurs in certain cells or even in one cell of the entire population, the modifications being provoked by agencies having no direct relevance to any adaptive changes involved. Mutations caused by ultra-violet light would come under this heading. They usually deprive a cell of a character which it originally possessed. In such a case they do not have any adaptive value, since the mere loss of a property could hardly enable a cell to compete more effectively with its unchanged neighbours. Changes could also be provoked by unusual thermal activation, encounters with chance impurities, and so on. If they happen to render the cell better suited for growth in some new medium, then in such a medium it can outgrow the unmodified types in such a way as to show what amounts to an adaptive response of the population as a whole. The regain of their lost properties by ultra-violet mutants *could* be due to this.

B. Large numbers or indeed all the cells suffer a direct modification as a result of their growth in changed conditions.

The mechanisms of 2A and 3A include all possible physical and chemical agencies which are capable of affecting molecular structure or indeed colloidal form. Any relation of the agency to the final biological result is caused merely by selection of forms which happen to be favoured by particular media.

The mechanisms of 2B and 3B are of greater interest from the physico-chemical point of view, since we have to show how adaptive responses can arise.

Case 2B might conceivably be analogous to the activation of a heterogeneous catalyst which occurs when it is repeatedly made to catalyse the same reaction. In this process the microcrystalline structure and possibly even the lattice spacings of a solid catalyst are gradually dragged into that configuration which gives an easy adsorption of (and so favours the formation of) the product of reaction. The analogy of enzymes and heterogeneous catalysts is too close for this possibility to be entirely neglected.

Case 3B is the hypothesis which has been explored in detail in this laboratory. Cells utilise very varied substrates to build up the same constituents of their mass. There must be a considerable number of alternative metabolic routes, and these will involve the utilisation of various enzyme systems to different extents. Now it may be shown that, since the effective combinations of enzyme systems reproduce themselves in the course of cell growth, there must be a linking of the functioning and the synthesis of enzymes, and that the enzyme proportions which are synthesised in a given medium will attain that value which corresponds to the optimum rate of growth. This provides for an automatic adaptive response (Hinshelwood and Lewis, *Proc. Roy. Soc.*, 1948, *B*, **135**, 316; Hinshelwood, " Chemical Kinetics of the Bacterial Cell," Oxford, 1946).

What should be specially emphasised (and it is not always realised) is that there is considerable similarity in some respects between 3A and 3B. As regards the total bacterial mass the results are identical. In the one case certain parts of the population increase relatively to the others : in the alternative case certain parts (already in existence) of each cell increase relatively to the rest. This identity in respect of total mass explains why the alternative hypotheses are difficult to choose between experimentally.

It is necessary at this stage to point out that the whole chemical question cannot be ruled out of court by the familiar objection that acquired characters cannot be transmitted, as adaptive changes in fact often are, and that, therefore, these cannot be really adaptive. If the character in the cell had to have been present from all time, then cultures isolated from single cells could not show adaptive phenomena (and they certainly do). If all changes arise from

chance mutations (leaving the recombination phenomenon aside), then the properties dependent on the mutations are just as much acquired as any which arise from changed enzyme proportions caused in turn by such agencies as altered reaction rates. There remains indeed the question whether the modification is independent of, or caused by, the agent towards which its effect later becomes manifest. But this is logically quite unrelated to any considerations about the inheritance of acquired characters. The principle of non-inheritance properly applies to the usual absence of any effect upon germ cells of nutrition, exercise, or mutilation of the entire animal or plant in which they are formed. The reproduction of such organisms is entrusted to special cells to which the acquired characters of the whole body are almost entirely irrelevant. To extend the non-inheritance principle to unicellular organisms which are their own germ cells, and which simply divide into two parts when they multiply is virtually to assert that reproductive mechanisms know how a change is caused in a cell and that they will refuse to copy it if it is induced, but are ready to do so if it is due to chance.

The discussion of the chemical basis of cell changes may therefore be regarded as a purely technical question, not to be prejudged by this general principle.

In the light of the above discussion and classification we propose to examine in detail some of the chemical phenomena which occur when mutations are induced in *Bact. lactis aerogenes* (*Aerobacter aerogenes*). Among other things we shall be concerned with the mechanism of the recovery of lost biochemical characters under defined chemical conditions. We shall also be concerned with the question whether the loss and recovery of properties is gradual and quantitative or abrupt and qualitative, a matter which possesses interest from the standpoint of any kind of theory.

PHYSICAL CHEMISTRY LABORATORY, OXFORD UNIVERSITY. [*Received, October 31st,* 1950.]

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260. *Induced and Other Variations in Bacterial Cultures. Part II. General Survey of Changes Produced in* Bact. lactis aerogenes (Aerobacter aerogenes) *by Ultra-violet Light and Some Other Mutagenic Agents.*

By A. C. R. DEAN and SIR CYRIL HINSHELWOOD.

A general survey is made of the changes induced in *Bact. lactis aerogenes* by exposure to ultra-violet light, to radiation from ^{35}S, and to certain chemical agents (proflavine and Fenton's reagent).

A significant proportion of mutants only appears when the fraction of survivors is very small. The chief effects are (*a*) reduction in growth rate in a minimal medium, and (*b*) modification of sugar-fermentation tests.

An almost continuous spectrum of behaviour is manifested.

Specific amino-acid requirements seldom appeared and were never absolute with this organism (which is normally very non-selective as regards nitrogen source).

THERE are numerous reports in the literature that mutations have been induced in bacteria by radiations (ultra-violet light, *X*-rays, α-, β-, and γ-rays) and by drugs. These mutants differ from the normal organism in various ways. Two main classes are "nutritional" and "fermentative" mutants. The former are unable to grow in the medium in which the untreated organism grows unless this medium is supplemented by one or more growth factors or amino-acids, whilst the latter are unable to carry out the fermentation reactions characteristic of the normal organism.

The object of this research was to treat *Bact. lactis aerogenes* (*Aerobacter aerogenes*) with various mutagenic agents, to examine the treated strains, and to investigate the manner in which any lost characters might be recovered.

This paper will be concerned in particular with an examination of the changes induced by ultra-violet irradiation, by the β- and γ-radiation from radioactive sulphur, and by proflavine and Fenton's reagent. It will take the form of a general survey of the changes induced by these agents. This is important, since although there have been many reports on their mutagenic action, there is little evidence as to whether the spectrum of changes induced in a bacterial population is continuous or discrete.

An investigation of the manner in which the recovery of any lost characters takes place will be described in the succeeding papers.

The Effect of Irradiation.—A series of experiments was carried out on a strain of *Bact. lactis aerogenes*, fully adapted to a simple synthetic medium, in which the viable count was progressively reduced by irradiation. The irradiation was carried out by the methods to be described later, and the survivors were plated out on a complete agar medium. This medium was chosen so that partly deficient and normal cells would both have opportunities for growth. From these experiments it was concluded that only when most of the organisms had been killed (fraction surviving 10^{-7} to 10^{-8}) did an appreciable fraction of the survivors exhibit deviations from the biochemical reactions characteristic of the aerogenes group, and abnormal growth rates in the synthetic medium. Accordingly a series of experiments was carried out in which the irradiation was continued until the bacterial population was reduced from 10^9 per ml. to between 20 per ml. and 2 per ml. The suspensions were plated out and screened (see Lederberg and Tatum, *J. Biol. Chem.*, **1946**, **165**, 381) and all the strains which this technique indicated as mutants were tested for growth in the synthetic medium and for their biochemical reactions ("The Bacteriological Examination of Water Supplies," Min. of Health Rep. on Public Health and Medical Subjects, No. 71, 1939, p. 36). Results are summarised in Table I.

TABLE I.

Mutant no.	Growth in synthetic medium. lag (hrs.).	m.g.t. (mins.).	Biochemical reactions. M.R.	V.P.	Indole.	Citrate.	Sucrose.	Dulcitol.	Group in classification.
Parent	—	33	—	+	—	+	A.G.	—	—
14	∞	—	—	+	—	+	A	—	1
16	∞	—	—	—	—	—	—	—	1
20	20	39	—	+	—	+	A.G.	—	2
21	48	47	—	—	—	—	A	—	3*b*
22	33	78	—	—	—	—	A	—	3*b*
23	60	56	—	—	—	—	—	—	3*b*
24	16	50	—	—	—	—	A	—	3*b*
25	∞	—	—	—	—	—	—	—	1
26	∞	—	—	—	—	—	A	—	1
27	16	41	—	+	—	+	A.G.	—	2
28	∞	—	—	+	—	—	A	—	1
29	16	46	—	—	—	+	—	—	3*b*
30	16	46	—	—	—	+	—	—	3*b*
31	∞	—	—	—	+	—	A	—	1
32	9	78	—	+	—	+	A.G.	—	3*a*
33	9	48	—	+	—	+	A.G.	—	3*a*
34	14	31/94 *	—	—	—	+	—	—	3*b*
35	12	47/150 *	—	—	—	+	—	—	3*b*
36	3	44	—	—	—	+	—	—	3*b*
38	8	28	—	+	—	+	A.G.	—	3*a*
39	11	42	—	—	—	+	—	—	3*b*
41	11	39	—	—	—	+	—	—	3*b*
42	3	49	—	—	—	+	—	—	3*b*

A = acid. M.R. = Methyl-red test.
A.G. = acid and gas. V.P. = Voges–Proskauer reaction.

Nos. 14, 16, 25, 26, 28, and 31 grew in synthetic medium after one sub-culture in asparagine–glutamic acid medium. The lags in the synthetic medium were 15, 3, 2, 6, 12, and 2 hours, and the mean generation time 350, 72, 65, 58, 44, and 44 minutes, respectively.

* = composite growth curve (segments of slower and then faster growth).

On the basis of these results the strains may be classified into three groups:

1. Members of this group were unable to grow in the synthetic medium when inoculated directly from broth. They grew in a medium containing asparagine and glutamic acid as nitrogen and carbon sources, and after one sub-culture in the latter were able to grow in the synthetic medium, at first with an increased mean generation time and low total population. Biochemical tests were abnormal.

2. In this group biochemical tests were normal. Growth took place in the synthetic medium on inoculation from broth, but with mean generation time higher and total population lower than normal.

3. The strains in this group were able to reach normal total populations in the synthetic medium, but the mean generation time was high. Biochemical tests were either normal or abnormal (sub-groups *a* and *b* respectively).

The distribution of the 23 strains among groups 1, 2, 3*a*, and 3*b* was 6, 2, 3, and 12.

It is interesting to note that of the 23 strains isolated 18 had abnormal biochemical reactions, namely, all 18 were unable to ferment sucrose, 16 did not give a positive Voges–Proskauer reaction (acetylmethylcarbinol formation), and 9 had lost the ability to grow with citrate as carbon source. The abnormal biochemical reactions were not consistent within the groups of the classification, and there appears to be no direct correlation between these abnormal reactions and the growth rate, since although in 18 strains in which the biochemical tests were abnormal the growth rate was also abnormal, there were 5 other strains in which the biochemical reactions were normal but the growth rate abnormal.

Mean generation times for the series of strains, with one exception, No. 14, whose mean generation time was 350 minutes, ranged from 30 to 80 minutes, the greatest frequency falling within the range 40—50 minutes. Lags were usually longer than normal (up to 60 hours) or else infinite (group 1). In the latter case one sub-culture in the asparagine–glutamic acid medium sufficed to make growth in the normal synthetic medium possible. No strain was isolated which did not grow easily in this asparagine–glutamic acid medium. This is in agreement with the results of Peacocke and Hinshelwood (*Proc. Roy. Soc.*, 1948, *B*, **135**, 456). Morrison and Hinshelwood (*J.*, 1949, 384) have suggested that the long lags obtained with *Bact. coli* when first transferred to an ammonium salt synthetic medium are due to the inability of the organism to form four- and five-carbon-atom compounds from glucose at an adequate rate. Since these substances are required at definite concentrations before growth can proceed, the apparent inability to utilise ammonia arises. This difficulty is ultimately overcome with *Bact. coli* during a long lag phase, but with the members of group 1 it is never overcome until the enzyme systems have been expanded by growth which has to be aided by the addition of glutamic acid and asparagine.

Enzyme Deficiencies in Irradiated Cells.—Table I shows that in the 23 strains isolated three types of behaviour in sucrose fermentation tests were observed, namely, the normal, where the end products were acid and gas, an intermediate type in which acid alone was produced, and a third type in which there was no interaction at all. It seemed desirable to investigate this behaviour further with other sugars. Accordingly four strains were selected—two in which acid was produced from sucrose, and two in which there was no reaction—and their ability to ferment a wide range of sugars was examined. The results are summarised in Table II.

TABLE II.

Sugar.	Normal *Bact. lactis aerogenes.*	Mutant. No. 14.	No. 16.	No. 22.	No. 23.
D-Arabinose	A.G.	—	—	—	—
Xylose	A.G.	—	—	—	A
Raffinose	A.G.	—	—	—	—
Glucose	A.G.	A	A	A	A
Mannose	A.G.	A	A	A	A
Galactose	A.G.	A	A	A	—
Sucrose	A.G.	A	—	A	—
Maltose	A.G.	A	A	A	—
Lactose	A.G.	A	A	A	—
Cellobiose	A.G.	—	—	A	—
Melibiose	A.G.	—	—	—	—
Inositol	A.G.	—	—	—	—
Sorbitol	A.G.	A	A	A	—
Rhamnose	A.G.	—	A	—	—

Results after 72 hours.

The pattern of the fermentation reactions is essentially similar with strains No. 14, No. 16, and No. 22; glucose, mannose, galactose, sucrose, maltose, and lactose can generally be metabolised to produce acid but no gas; the less common substances, D-arabinose, xylose, raffinose, cellobiose, melibiose, inositol, and rhamnose are not metabolised. Strain No. 23 is exceptional.

A normal strain of *Bact. lactis aerogenes* is capable of fermenting the 14 sugars tested in a short time; all the sugars yield acid and gas within 24 hours, except D-arabinose, which does so within about 48 hours. If the enzymes acting on these substrates are all present in the normal organism, *i.e.*, are constitutive enzymes (*vide* Karstrom, *Ann. Acad. Sci. Fenn.*, 1930, Ser. *A*, Vol. 33, No. 2) it is thus necessary to postulate the absence of 8, 8, 7, and 12 enzymes

respectively with strains 14, 16, 22, and 23. Consideration of the generally accepted scheme for the fermentation of sugars, *viz.*:

$$\text{Sugar} \longrightarrow \text{hexose diphosphate} \longrightarrow \text{dihydroxyacetone or phosphoglyceraldehyde} \xrightarrow{\text{dehydrogenase}}$$

$$\text{phosphoglyceric acids} \xrightarrow{\text{enolase}} \text{phospho-enol pyruvic acid} \longrightarrow \text{pyruvic acid} \longrightarrow CO_2$$

will elucidate this statement. When the sugar is not metabolised at all, the enzymes responsible for transforming that sugar into hexose diphosphate are probably absent, *i.e.*, with No. 14 raffinase (or emulsin), cellobiase, melibiase, arabinase, rhamnase, xylase, and inositolase are absent. In the case of the sugars where acid was produced, but no gas, the same enzyme might be absent in each case. This hypothesis was confirmed by further investigation of strain No. 14. It was capable of growing normally with pyruvic acid as carbon source, but not with glycerol. This suggests that the missing enzyme may be the enolase.

To recapitulate, it is seen that in the tests with 14 sugars between 8 and 12 constitutive enzymes would be absent. This number can be increased when the other abnormal biochemical reactions in Table I are considered, and could probably be shown to be still greater if other substrates were tested.

TABLE III.

Summary of ultra-violet light experiments.

Expt. no.	Time of irradiation (hours).	Survivors, minimal medium agar.	Survivors, heart broth agar (additional to those on minimal medium agar).	Fermentative mutants.	Nutritional mutants.
1*a*	3	0	0	0	0
b	3	0	1	1	0
c	3	1	3	1	0
2*a*	3	0	0	0	0
b	3	0	0	0	0
c	3	0	0	0	0
3	3	29	3	1	0
4*a*	2	0	0	0	0
b	2	0	1	1	0
c	2	0	0	0	0
d	2	1	0	0	0
5*a*	1·5	0	2	2	0
b	1·5	1	4	3	0
c	1·5	2	1	1	0
6*a*	3	10	8	6	0
b	3	14	5	3	0
7	3	2	1	1	0
8*a*	3 *	84	2	not tested	0
b	3 *	8	4	" "	0
c	3 *	14	0	" "	0
d	3 †	not screened	0	" "	0
e	3 †	" "	2	" "	0
f	3 †	" "	1	" "	0
g	3 †	" "	1	" "	0
h	3 †	" "	1	" "	0
i	3 †	" "	1	" "	0
j	3 †	" "	2	" "	0
k	3 †	" "	5	" "	0
9*a*	3 *	21	1	" "	0
b	3 *	25	0	" "	0
c	3 †	not screened	80	" "	0
d	3 †	" "	8	" "	0
10*a*	3 †	5	0	0	0
b	3 †	0	0	0	0
c	3 †	0	0	0	0
d	3 *	74	1	not tested	0
e	3 *	0	0	" "	0
f	3 *	45	0	" "	0
g	3 *	39	0	" "	0
h	3 *	9	1	" "	0
i	3 *	11	0	" "	0
j	3 *	10	0	" "	0

TABLE III—*continued.*

Expt. no.	Time of irradiation (hours).	Survivors, minimal medium agar.	Survivors, heart broth agar (additional to those on minimal medium agar).	Fermentative mutants.	Nutritional mutants.
11*a*	3	0	0	0	0
b	3	0	0	0	0
c	3	0	0	0	0
d	3	1	0	0	0
e	3	0	0	0	0
f	3	0	0	0	0
g	3	1	0	0	0
h	3	0	0	0	0
i	3	0	0	0	0
j	3	1	0	0	0
k	3 *	5	0	0	0
l	3 *	20	0	0	0
m	3 *	ca. 500	0	0	0
n	3 *	3	0	0	0
o	3 *	47	0	0	0
p	3 *	4	0	0	0
q	3 *	0	0	0	0
r	3 *	ca. 500	0	0	0
s	3 *	ca. 500	0	0	0
12*a*	3 *	24	1	not tested	0
b	3 *	22	0	" "	0
c	3 †	not screened	40	" "	0
d	3 †	" "	48	" "	0
13*a*	3 *	74	1	" "	0
b	3 *	9	1	" "	0

Total number of plates = 67. Number of colonies tested = 230.

* Incubated in broth after irradiation.

† Incubated in broth after irradiation and treated with penicillin.

Alternatively, it is possible that the missing enzymes are adaptive, *i.e.*, are formed only in the presence of the substrate. The damage caused by the irradiation would therefore have resulted in the impairment of the ability of the cell to form adaptive enzymes. The alternatives will be discussed more fully later.

It is of interest to draw attention here to some biochemical variants in the *coli–aerogenes* group which have been described in the literature.

Bergey ("Manual of Determinative Bacteriology," Baillière, Tindall, and Cox, London, 1948, p. 446) reports a strain *Esch. intermedium*, which may produce acid or acid and gas from the sugars in Table II, whilst Prescott, Winslow, and McCrady ("Water Bacteriology," Wiley, New York, 1946, p. 202) describe four groups, micro-aerogenic, pseudo-micro-aerogenic, anaerogenic, and non-lactose-fermenting coliforms. Micro-aerogenic coliforms may be variants of *Esch. coli*, *Aerobacter*, or intermediate organisms, which produce from a bubble to 10% of gas from lactose in 48 hours at 37°. Pseudo-micro-aerogenic coliforms may or may not produce gas from lactose. Anaerogenic coliforms produce acid and no gas from lactose. Non-lactose-fermenting coliforms may be *Esch. coli*, *Esch. freundii*, or *Aerobacter* in type.

Nutritional Mutants.—The technique used in the experiments reported in this paper, although devised for the isolation of nutritional mutants, has yielded only fermentative mutants. Indeed, many of these fermentative mutants, those which produced acid but no gas, would have been missed if the usual methods for their detection, *i.e.*, plating on agar containing sugar and indicator, before or after irradiation, had been followed. It will be remembered that the strains were isolated by screening, *i.e.*, by plating on a minimal medium, adding a complete medium, and collecting only those colonies which appeared after addition of the latter. By this method strains were isolated which could be classified into groups, one of which (group 1) contained organisms which would only grow in the normal synthetic medium after one passage through amino-acids or asparagine–glutamate medium. It is probable that all the strains originally had a similar requirement, but that this was overcome through growing in the presence of the complete medium in all but the extreme cases (group 1). Alternatively, it may be that all the strains except group 1 would have grown on minimal agar, but with a longer lag than the experiments allowed.

From the literature on this subject it appears that two explanations may be given for the non-appearance of nutritional mutants in the experiments carried out so far, namely, (*a*)

insufficient strains were tested, and (*b*) appreciable growth of the irradiated strains was not allowed to take place before plating (*vide* Demerec and Latarjet, *Cold Spring Harb. Symp. Quant. Biol.*, 1946, **11**, 38).

A series of irradiations was carried out in which these conditions were satisfied. At the same time Davis's technique (*J. Amer. Chem. Soc.*, 1948, **70**, 4267) for concentrating nutritional mutants by the action of penicillin was also investigated. Results are summarised in Table III.

There was again a complete absence of nutritional mutants even when a period of proliferation in broth had been allowed before plating, or when the penicillin method had been used. A series of strains from one of these irradiation experiments was inoculated into the normal synthetic

TABLE IV.

The examination of strain No. 52 for nutritional deficiencies.

Supplement added to synthetic medium.	Lag (hours) before growth began.	Supplement added to synthetic medium.	Lag (hours) before growth began.
Broth	10	Biotin	51
Asparagine–glutamic acid ...	16	Adenosine	51
Tryptophan	27	All amino-acids	144
Leucine	30	Arginine	168

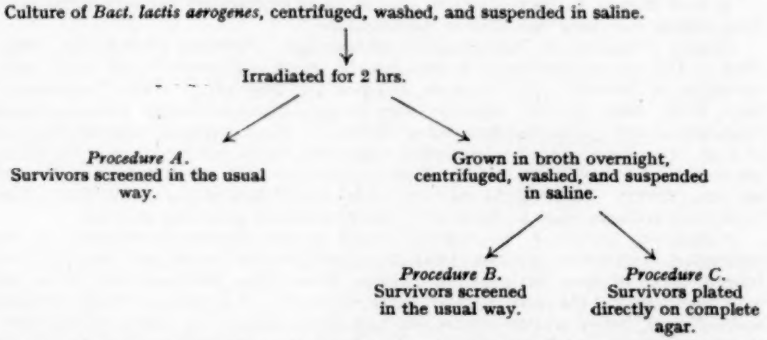
No growth took place in the control (no supplements) or with the following supplements, during 12 days:

asparagine	hydroxyproline	pyridoxin
histidine	tyrosine	guanine
glutamine	methionine	D-ribose
*iso*leucine	aspartic acid	inositol
valine	histidine + nicotinic acid	biotin + nicotinic acid + calcium D-pantothenate + *p*-aminobenzoic acid + aneurine + pyridoxine + adenosine + guanine + D-ribose + inositol.
lysine	nicotinic acid	
serine	calcium D-pantothenate	
threonine	*p*-aminobenzoic acid	
cysteine	aneurine	

(The amino acids are in most cases D–L mixtures.)

medium from broth; the mean generation times were found to be: 30, 33, 43, 43, 48, 50, 50, 53, 56, 56, 57, 58, 59, 60, 70, 72, 99, and 115 minutes. It will be seen that they present a continuous spectrum of mean generation times (as do the fermentative mutants).

A further experiment was carried out and, since it was more detailed than the others, the procedure used is represented in the annexed diagram.


Culture of Bact. lactis aerogenes, centrifuged, washed, and suspended in saline.
Irradiated for 2 hrs.
Procedure A.
Survivors screened in the usual way.
Grown in broth overnight, centrifuged, washed, and suspended in saline.
Procedure B.
Survivors screened in the usual way.
Procedure C.
Survivors plated directly on complete agar.

From these three procedures 112 strains were isolated and were tested for their ability to grow in the normal medium and for sucrose fermentation. Of them, 91% were fermentative mutants, and the distribution of these was independent of the procedure used for their isolation; 22% of these fermentative mutants produced acid and a small volume of gas from sucrose, a type of behaviour which would suggest that the enzymes responsible for gas production had only been partly damaged in some cases, and which could be explained by the shorter period of irradiation. Examination of several strains isolated by each procedure with the wide range of sugars used previously, indicated much the same pattern as in the earlier experiments.

Of the 12 strains, only one (No. 52) was unable to grow in the normal synthetic medium. It had been isolated by procedure *C*. It was then inoculated into the normal synthetic medium

supplemented by a wide range of amino-acids and growth factors, both singly and in admixture (Table IV). Growth took place first in broth (10 hours) and then in the synthetic medium supplemented by the various amino-acids. The order was: asparagine and glutamic acid (16 hours), tryptophan (27 hours), leucine (30 hours), biotin (51 hours), adenosine (51 hours), a mixture of all the amino-acids (144 hours), and arginine (1 week). In other words, according to the time limit allowed for the test, various nutritional requirements could have been postulated. This strain, like the other members of group I, was capable of growth in the normal synthetic medium after one sub-culture in asparagine–glutamic acid.

There are considerable discrepancies in the literature regarding the standards to be adopted when testing for nutritional mutants. For example, Lederberg (*Ann. Rev. Microbiol.*, 1949, **3**, 1) describes such mutants as having reproducible specific nutritional requirements. Reaume and Tatum (*Arch. Biochem.*, 1949, **22**, 336) define a yeast which will grow in 70—100 hours in the absence of a growth factor, but which will grow more rapidly in its presence, as having a "partial requirement," and a strain in which growth is delayed beyond 100 hours as having an "absolute requirement." With the same organism Lindegren ("The Yeast Cell—Its Genetics and Cytology," Educational Publ., Saint Louis, 1949) has found that in most cases prolonged incubation of an apparently deficient culture has finally resulted in full growth—in other words, relative differences in capacity for synthesis are encountered more often than absolute differences. With mutants of *B. subtilis* Teas (*J. Bact.*, 1950, **59**, 103) allowed 60 hours as the time limit, whilst with a histidine-requiring mutant of *Bact. coli* Ryan and Schneider (*ibid.*, 1948, **56**, 699) obtained a maximum growth in 12 hours with 25 μg. of histidine per ml. and in 24 hours in the absence of the amino-acid. Further sub-culture in the absence of histidine resulted in normal growth in 12 hours. A similar case is reported by Bonner, Tatum, and Beadle (*Arch. Biochem.*, 1943—44, **3**, 82) with a mutant of *Neurospora* which was said to require *iso*leucine and valine, but to adapt itself in time so that it was able to grow on media containing neither. The authors postulate that in this case the strains are capable of making the required substance by an alternative mechanism, thereby circumventing the genetic block.

TABLE V.

Growth rates and biochemical properties of Bact. lactis aerogenes *treated with β- and γ-radiation from* ^{35}S.

Strain.	1st sub. in synth. medium: lag (mins.).	m.g.t. (mins.).	M.R.	V.P.	Indole.	Citrate.	Sucrose.	Dulcitol.
1	320	47	—	—	—	+	A	—
2	602	39	—	—	—	+	—	—
3	600	41	—	—	—	+	—	—
4	510	38	—	—	—	+	—	—
5	680	40	—	—	—	+	A	—
6	770	37	—	—	—	+	—	—
7	920	40	—	—	—	+	—	—
8	466	44	—	—	—	+	—	—
9	474	35/56 *	—	—	—	+	—	—
10	450	31/48 *	—	—	—	+	—	—
11	808	45	—	—	—	—	A	—
12	510	43	—	—	—	+	—	—
13	763	37	—	—	—	+	—	—
14	418	32/40 *	—	—	—	+	—	—
15	462	38	—	—	—	+	—	—
16	450	27/48 *	—	—	—	+	—	—
17	330	34/53 *	—	—	—	+	—	—
18	290	40/90 *	—	—	—	+	—	—
19	640	40	—	—	—	+	—	—
20	465	45	—	—	—	+	—	—
Control	—	31	—	+	—	+	A.G.	—

* Composite growth curve.

Returning to our strain No. 52 it will be seen that, according to the time limit set for the experiment, various nutritional requirements could have been ascribed to it. Spontaneous reversion of mutants would not explain the results unless this were assumed only to take place in the tubes in which growth occurred. The strain which grew in asparagine–glutamic acid was sub-cultured into the normal synthetic medium, and after two sub-cultures in the latter had a mean generation time of 52 minutes, and after six sub-cultures a mean generation time of

39 minutes, as compared with the normal value of 33 minutes. In other words, it was not a normal organism, and thus reversion in the ordinary sense could not have occurred. A more probable explanation for the behaviour would be that either the various amino-acids or impurities in them have specific influences in reducing the lag.

The Effect of Other Mutagenic Agents on Bact. lactis aerogenes.—*Use of* $^{35}SO_4$. A culture of *Bact. lactis aerogenes* was grown in the normal synthetic medium in which the sulphur was supplied as $^{35}SO_4$. This would subject the organisms to the β- and γ-radiations from ^{35}S both during and after the assimilation of the sulphate. When growth had ceased, dilutions were plated out in the normal manner on complete agar, twenty colonies were transferred to broth and tested for

TABLE VI.

Growth rates and biochemical properties of Bact. lactis aerogenes *treated with proflavine, 260 mg./l.*

Strain.	1st sub. in synth. medium: lag (mins.).	1st sub. in synth. medium: m.g.t. (mins.).	Biochemical tests. M.R.	V.P.	Indole.	Citrate.	Sucrose.	Dulcitol.
1	546	41	—	—	—	+	—	—
2	660	45	—	—	—	+	—	—
3	590	45	—	—	—	+	—	—
4	218	46	—	—	—	+	—	—
5	450	38	—	—	—	+	—	—
6	524	37	—	—	—	+	—	—
7	445	35	—	—	—	+	—	—
8	540	48	—	—	—	+	—	—
9	524	37	—	—	—	+	—	—
Control	—	29	—	+	—	+	A.G.	—

TABLE VII.

Growth rates and biochemical properties of Bact. lactis aerogenes *treated with Fenton's reagent* (80 *mg. of* $FeSO_4.7H_2O$ *per l.*; 240 *mg. of* H_2O_2 *per l.*).

Strain.	1st sub. in synth. medium: lag (mins.).	1st sub. in synth. medium: m.g.t. (mins.).	Biochemical tests. M.R.	V.P.	Indole.	Citrate.	Sucrose.	Dulcitol.
1 *Hour's treatment.*								
1	480	35	—	+	—	+	A.G.	—
2	169	52	—	+	—	+	A.G.	—
3	180	46	—	—	—	—	—	—
4	655	75/45 *	—	+	—	+	A.G.	—
5	3510	50/41 *	—	—	—	—	A	—
6	2237	51/38 *	—	—	—	+	—	—
7	672	37	—	+	—	+	A.G.	—
8	658	36	—	+	—	+	A.G.	—
9	294	46	—	+	—	+	A.G.	—
10	278	31	—	+	—	+	A.G.	—
2 *Hours' treatment.*								
1	740	46	—	—	—	+	—	—
2	728	50	—	—	—	+	—	—
3	604	58	—	—	—	+	—	—
4	719	53	—	—	—	+	—	—
5	677	67	—	—	—	+	—	—
6	680	66	—	—	—	+	—	—
7	570	50	—	—	—	+	—	—
8	540	40	—	—	—	+	—	—
9	563	57	—	—	—	+	—	—
10	567	53	—	—	—	+	—	—
Control	—	31	—	+	—	+	A.G.	—

* Composite growth curve.

growth in the normal synthetic medium and for their fermentative abilities by the methods described previously. Results are recorded in Table V. The mean generation times, as in the ultra-violet irradiation experiment, were all greater than normal, although the range was not so great. Biochemical tests, too, showed similar abnormalities.

Proflavine. Treatment with proflavine sulphate reduced the bacterial population from 10^9 to 10 per ml. The survivors were plated out on complete agar and were subjected to the usual tests (Table VI).

Fenton's reagent. This reduced the viable count of the organism from 10^9 per ml. to 40 and 10 per ml. after 1 and 2 hours' interaction respectively. Definite volumes were plated out on complete agar, and the survivors tested in the usual manner. The mean generation times and biochemical reactions of the survivors were again abnormal, the degree of abnormality increasing with time (Table VII).

Sulphanilamide. Kohn and Harris (*J. Bact.*, 1942, **44**, 717) rendered a strain of *Bact. coli* permanently exacting towards methionine by training it to sulphanilamide in the presence of methionine. After 30 sub-cultures a permanently exacting strain was stated to be obtained. When the experiment was repeated with *Bact. lactis aerogenes* the organism was not exacting towards methionine.

The action of β- and γ-radiation, Fenton's reagent, and proflavine on *Bact. lactis aerogenes* has, like ultra-violet radiation, resulted in the production of cells with abnormal biochemical characteristics and increased growth rates.

Fenton's reagent inactivates enzymes, and it seems that the hydroxyl radical may be necessary, since both Fe^{++} and hydrogen peroxide are inactive alone (Collinson, Dainton, and Holme, *Nature*, 1950, **165**, 266). Ultra-violet radiation may act on bacteria through the agency of hydroxyl radicals, and so it is not surprising that both it and Fenton's reagent produce the same effects.

It is interesting to note that a behaviour similar to that induced by proflavine in these experiments has been reported by Penfold (*J. Hyg., Camb.*, 1913, **13**, 35). A strain of *Bact. coli* was grown in nutrient agar containing sodium chloroacetate, and papillæ were produced which were resistant. Cultures from these papillæ were unable to form gas from sugars. Lederberg (*Heredity*, 1948, **2**, 177) has repeated the experiments, and has shown that the cells were blocked in the dissimilation of pyruvate. This is similar to the effect of ultra-violet light on *Bact. lactis aerogenes* (see above). Lederberg's explanation is that the chloroacetate simply selects spontaneous resistant mutants, but he admits that the specific connection between chloroacetate resistance and biochemical deficiencies is enigmatic. It seems more reasonable to postulate that the chloroacetate, by interacting with the enzymes, produces biochemical deficiencies. The postulate that direct injury to the cellular enzymes by a drug produces resistance is repudiated by the same author (*Ann. Rev. Microbiol.*, 1949, **3**, 1) on the grounds that, since the metabolic changes persist on cultivation in drug-free medium, the susceptible enzymes would have to be autocatalytic. But this autocatalytic property is indeed possible when one considers the enzyme systems of the bacterium as a whole. Proflavine forms electro-absorption complexes with nucleo-proteins, and streptomycin inhibits the metabolism of nucleic acids (Robson and Keele, " Recent Advances in Pharmacology," Churchill, London, 1950, p. 164). Streptomycin has been reported to inhibit benzoic acid oxidation in sensitive mycobacteria and the effect has been shown to be connected with the adaptive formation of oxidative enzymes (Fitzgerald, Bernheim, and Fitzgerald, *J. Biol. Chem.*, 1948, **175**, 195). It is possible that proflavine also interferes with adaptive-enzyme formation by interfering with nucleic acid metabolism. It is significant that one of the strains after proflavine treatment had a pattern of biochemical reactions similar to that of strain No. 16 when tested with a wide range of sugars.

Conclusion.—It is of considerable interest in connexion with the general classification outlined in Part I to consider whether the damage wrought in the cell by the mutagenic agents in these experiments is highly specific, stepwise, and qualitative, as it would be if changes occurred discontinuously in localised, more or less independent parts of the cell structure (as the most primitive view of a gene might suggest); or whether, on the other hand, it is continuously graded and of a quantitative rather than a qualitative character, as it would be if various parts of the cell pattern suffered greater or smaller change.

From the purely experimental point of view the results by themselves are certainly more suggestive of the latter than of the former. Growth rates of the mutants show a continuous spectrum of values. Sugar reactions may be slowed (small gas) or inhibited (no gas). The nutritional mutant isolated could have been assigned almost any set of " requirements " according to the precise condition of the test applied.

All that we shall conclude from this at the present juncture is that if one wishes to interpret the changes in cell pattern in these particular experiments on a rigid " gene-present : gene-absent " basis, then the number and degree of interaction of these genes must be such as to give rise to an almost continuous range of possibilities.

Experimental.

Materials.—Organism. A strain of *Bact. lactis aerogenes* was maintained by serial sub-culture in a stream of sterile air at 40° in a synthetic medium. The biochemical reactions of this strain are described in Tables I and II.

Synthetic medium. This was prepared by mixing sterile solutions of glucose (50 g. per l.), phosphate buffer (9 g. of potassium dihydrogen phosphate per l., plus sufficient sodium hydroxide to make the pH 7·12), ammonium sulphate (5 g. per l.), and magnesium sulphate (1 g. per l.) under aseptic conditions and in the ratios 10 : 10 : 5 : 1.

Asparagine–glutamic acid medium. The ammonium sulphate and glucose in the synthetic medium were replaced by asparagine and glutamic acid at concentrations of 0·38 and 0·27 g. per l. respectively.

Minimal medium agar. A minimal medium made by solidifying the synthetic medium with 1·5% of agar.

Complete agar. Heart-broth agar was chosen since it is likely to contain all the growth factors required by any possible mutants.

Production of Mutants.—Ultra-violet irradiation. A fully grown culture of the organism was centrifuged, then washed three times in saline, and the cells were suspended in sufficient saline to give a population of 10^9/ml. About 18 ml. of the suspension were transferred to a quartz tube, 2 cm. in diameter, and irradiated at room temperature by a mercury-vapour lamp emitting most of its energy in the range 2540—2800A. (the range in which bactericidal action is greatest) until the viable count had been sufficiently reduced. This was tested by withdrawing samples at intervals and plating them out on complete agar.

β- and γ-Radiation from ^{35}S. The organism was grown in the usual way in the synthetic medium in which the sulphur was supplied as $^{35}SO_4$.

Proflavine sulphate. A suspension of the organism in saline was prepared in the same manner as in the ultra-violet experiments. Proflavine sulphate was added to a concentration of 260 mg. per l. and allowed to act for 18 hours.

Fenton's reagent. Aqueous solutions of $FeSO_4.7H_2O$ and hydrogen peroxide were added to a suspension of the organism in saline to give concentrations of 80 and 240 mg. per l. respectively.

Sulphanilamide. The organism was serially sub-cultured in the synthetic medium in the presence of methionine (3×10^{-6}M.) and sulphanilamide. The concentration of the latter was increased from 350 to 3500 mg. per l. during 11 sub-cultures, and a further 30 sub-cultures were carried out at the higher concentration.

Isolation of Mutants.—The strains, after treatment with the various mutagenic agents, were either plated out directly or after further treatment. The method followed in each case is indicated in the text. When the colonies on the plates had reached a sufficient size they were transferred to "Lemco" broth in which they were stored.

Direct plating. Definite volumes of the treated suspensions were plated out on complete agar or were screened by the method of Lederberg and Tatum (*loc. cit.*), with normal agar as the minimal medium and heart-broth agar as the complete medium.

Plating after a period of growth in complete medium. One ml. of the treated suspension was inoculated into "Lemco" broth and incubated for 24 hours. The bacteria were then plated out on complete agar or were separated from the broth by centrifuging, washed three times with saline, and then screened.

Plating after treatment with penicillin. To a suspension in synthetic medium (after incubation in broth) was added penicillin G (sodium salt) to a concentration of 300 units per ml. The suspension was incubated at 40° and at intervals up to 20 hours samples were withdrawn and either plated directly on complete agar or screened.

Testing of Mutants.—Three loopfuls of the appropriate broth culture (of the order of 10^8—10^9 cells) were inoculated into the synthetic medium, and the latter was kept at 40° under aerobic conditions. If no growth took place the culture was inoculated into the asparagine–glutamic acid medium and, after one sub-culture in this medium, into the synthetic medium. No strains were isolated which did not grow in the asparagine–glutamic acid medium, and after one sub-culture in the latter growth took place in all cases in the synthetic medium.

The biochemical reactions of the strains were examined by the methods described in "The Bacteriological Examination of Water Supplies" (*op. cit.*).

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261. *Induced and Other Variations in Bacterial Cultures. Part III. Recovery of Normal Growth Rates by Slow-growing Mutants of* Bact. lactis aerogenes.

By A. C. R. Dean and Sir Cyril Hinshelwood.

The recovery of ultra-violet light-damaged mutants of *Bact. lactis aerogenes* to normal growth rate in a simple synthetic medium is studied quantitatively and the course of events compared with that expected on the basis of different theories.

It has been shown that all the strains of *Bact. lactis aerogenes* isolated after irradiation with ultra-violet light are capable of growth in the synthetic medium with varying growth rates (Part II, Table I). The interesting question arises whether these growth rates are constant for the particular strain, that is, whether the damage wrought by the ultra-violet light is irreparable, or whether the cells can be retrained to behave like normal organisms. The latter alternative proves to be true, since on serial sub-culture in the synthetic medium all the strains (23 in number) were eventually trained to the normal mean generation time, and when they were so trained their biochemical reactions were those of a normal *Bact. lactis aerogenes*. The quantitative study of the recovery process has been undertaken.

The experiments are summarised in Table I. Between 20 and 60 sub-cultures were usually necessary for training, during which the growth rate slowly increased. This recovery is, according to one point of view, suggestive of the repair and expansion of a damaged enzyme system. The alternative hypothesis is that spontaneous genetic mutation (reversion) may take place at some stage during the training process, resulting in cells with the normal mean generation time, and that these then outgrow the rest.

The effect of such spontaneous mutation on the shape of successive growth curves has been calculated for comparison with experiment.

Let n represent the number of slow-growing cells, m the number of back mutants, and ρ be the rate of back mutation (reversion). It is assumed that the formation of the back mutants does not appreciably reduce the number n at any time. We then have the equations

$$\mathrm{d}n/\mathrm{d}t = k_1 n$$
$$\mathrm{d}m/\mathrm{d}t = k_2 m + \rho \mathrm{d}n/\mathrm{d}t$$

Therefore

$$\mathrm{d}m/\mathrm{d}t = k_2 m + \rho k_1 n$$

and

$$\mathrm{d}m/\mathrm{d}t = k_2 m + \rho k_1 n_0 e^{k_1 t}$$

where n_0 is the value of n when $t = 0$.

The solution of the last equation is

$$m e^{-k_2 t} - m_0 = \frac{\rho k_1 n_0}{k_1 - k_2} \{e^{(k_1 - k_2)t} - 1\}$$

whence

$$m = \frac{\rho k_1 n_0}{k_2 - k_1} \{e^{k_2 t} - e^{k_1 t}\} + m_0 e^{k_2 t}$$

$$N_{\text{total}} = n + m$$

and, if $m_0 = 0$, we have

$$N_{\text{total}} = n_0 e^{k_1 t} + \frac{\rho k_1 n_0}{k_2 - k_1} \{e^{k_2 t} - e^{k_1 t}\}$$

Let $N_{\text{total}}/n_0 = \nu$ and $\rho k_1/(k_2 - k_1) = A$

Then

$$\nu = (1 - A)e^{k_1 t} + A e^{k_2 t}$$

In typical cases the mutant grows about half as fast as the original or the reverted form: we may therefore for purposes of illustration take $k_2 = 2k_1$. We shall also take the absolute values of k_1 and k_2 to correspond to mean generation times of 60 and 30 minutes respectively. The values of ν have been calculated as functions of time for various values of ρ, the magnitude of the latter being suggested by statements that reversion rates for *Bact. coli* mutants lie in this sort of range. (In Fig. 1 the curves *A*, *B*, and *C* correspond respectively to values of 10^{-5}, 10^{-6}, and 10^{-8} for ρ.)

TABLE I.

Training of irradiated strains. Mean generation times.

No. of subcultures in normal medium.	Type 1.					Type 2.	
No.:	16.	25.	26.	28.	31.	20.	27.
2	—	65	—	—	44	—	—
3	—	—	58	44	—	39	—
4	—	—	—	—	—	42	41
5	—	37	44	—	—	40	—
6	—	—	—	—	44	41	38
7	—	38	—	40	—	—	—
9	72	—	41	—	—	—	—
10	—	—	—	—	—	43	34
11	—	—	—	45	—	—	—
13	—	—	—	—	—	—	35
14	—	—	47	—	—	—	—
17	—	42	—	—	—	—	—
20	—	—	60	—	*34*	35	*33*
21	—	—	—	36	—	*32*	—
22	46	—	—	—	—	—	—
27	—	35	—	—	—	—	—
31	—	—	52	—	—	—	—
32	33 *	—	—	47	—	—	—
38	—	*33*	38	—	—	—	—
39	48	—	—	—	—	—	—
44	—	—	*33*	*31*	—	—	—
	34	—	—	—	—	—	—

	Type 3a.			Type 3b.										
No.:	32.	33.	38.	21.	22.	23.	24.	29.	30.	34.	35.	36.	39.	41.	42.
1	78	48	—	—	—	—	—	—	—	—	—	—	—	—	49
2	—	—	—	—	78	—	—	46	46	31/94 †	—	—	—	—	—
3	—	—	—	47	—	56	50	—	—	—	47/150 †	44	42	39	—
4	*33*	41	—	44	—	—	—	—	—	—	—	—	—	—	—
5	—	—	*28*	—	79	—	45	42	51	—	—	—	—	—	—
6	—	—	—	42	—	38	—	—	—	—	—	—	—	—	46
7	—	—	—	—	44	—	—	—	—	—	—	—	—	—	—
8	—	*30*	—	—	—	—	—	45	—	—	—	57	—	—	—
9	—	—	—	—	44	34	—	—	41	—	—	—	49	41	—
10	—	—	—	—	—	—	—	43	—	44	57	—	—	—	—
12	—	—	—	—	39	—	38	—	—	—	—	—	—	—	—
13	—	—	—	36	—	36	—	—	—	—	—	—	—	—	—
14	—	—	—	—	—	—	—	—	—	*31*	—	—	—	—	—
15	—	—	—	45	42	*33*	*33*	—	—	—	—	72	—	57	—
18	—	—	—	35	42	—	—	—	—	—	59	—	—	—	—
19	—	—	—	—	—	—	—	—	46	—	—	—	—	—	—
20	—	—	—	—	—	—	—	49		—	—	—	—	—	29
22	—	—	—	*32*	55	—	—	—	—	—	—	—	—	—	—
25	—	—	—	—	—	—	—	—	—	—	—	56	42	41	—
27	—	—	—	—	—	—	—	—	—	—	41	—	—	—	—
32	—	—	—	—	—	—	—	—	—	—	—	—	—	44	—
33	—	—	—	—	54	—	—	—	—	—	—	—	38	—	—
36	—	—	—	—	—	—	—	47	65	—	45	—	—	—	—
38	—	—	—	—	47	—	—	—	—	—	—	—	—	—	—
42	—	—	—	—	—	—	—	—	—	—	—	39	—	—	—
43	—	—	—	—	57	—	—	37	*31*	—	—	—	—	40	—
44	—	—	—	—	—	—	—	—	—	—	—	—	39	—	—
46	—	—	—	—	—	—	—	—	—	—	36	—	—	—	—
50	—	—	—	—	—	—	—	—	—	—	—	48	—	36	—
52	—	—	—	—	—	—	—	—	—	—	—	—	46	—	—
53	—	—	—	—	42	—	—	—	—	—	—	—	—	—	—
54	—	—	—	—	—	—	—	—	—	—	*34*	—	—	—	—
55	—	—	—	—	—	—	—	35	—	—	—	—	—	—	—
62	—	—	—	—	32	—	—	—	—	—	—	—	*34*	—	—
63	—	—	—	—	—	—	—	*34*	—	—	—	—	—	—	—
64	—	—	—	—	—	—	—	—	—	—	—	*33*	—	—	—
65	—	—	—	—	—	—	—	—	—	—	—	—	—	*32*	—

* Sugar reactions still incorrect. † Composite growth curve.

Italicised figures denote correct m.g.t. and correct sugar reactions.

In a normal growth curve there is during the period of active multiplication a linear relation between the time and the logarithm of the number of bacteria. The presence of reverse mutants leads to the bending of the growth curve as these outgrow the unchanged cells, and the result is a rather rapid fall in the mean generation time from 60 to 30 minutes. The value assumed for ρ affects the time at which the increase of slope occurs (Fig. 1), but not the rate at which it occurs when it once sets in. In the figures ν is plotted in such a way as to imply that unlimited multiplication of the culture is allowed to take place, without the interruption of serial subcultures. In fact, of course, the growth is interrupted by the serial transfers, a multiplication ratio of about 10^8 representing one subculture, as indicated by the horizontal

FIG. 1.

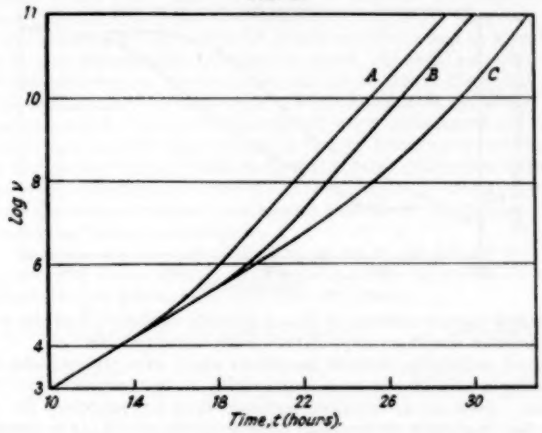
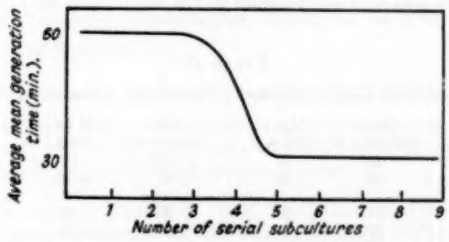


FIG. 2.



lines in Fig. 1. If a formal mean generation time is calculated from the mean slope of the curve of log ν against t, then the relationship of this mean generation time to the serial subculture number will be of the form shown in Fig. 2.

It appears that the change from the longer to the shorter mean generation time should take place in the course of a single subculture. To detect the transformation it is necessary to obtain growth curves for every subculture during the training process.

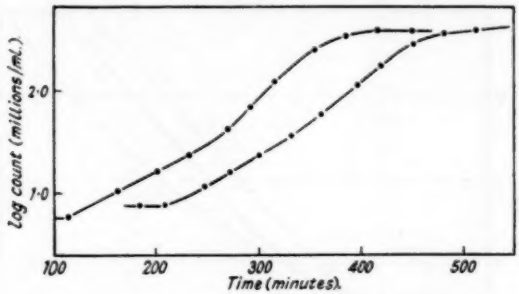
This experiment was carried out on strain No. 14 and the entire growth curve determined for every subculture up to 70 when training was complete. It will not be feasible to reproduce all the curves, but it may be stated that they were all of the normal logarithmic type or else of the type shown in Fig. 3. The mean generation times during training are given in Table II.

At first sight the curves in Fig. 3 are strongly suggestive of the theoretical form shown in Fig. 1, but the total picture of the retraining phenomenon does not accord with this conclusion. If there were a single reverse mutation which restored the normal cells, the transition from the slower to the more rapid growth would declare itself in the course of a given subculture and then be permanent. Actually there is a slow and gradually developing effect of training,

observable over very many subcultures (Table II). The composite growth curves appear at certain stages and then disappear, and whatever they indicate they do not represent an irreversible re-emergence of a fast-growing strain at one given stage.

If we assume that there are competing metabolic routes used by the cell, and that damaged enzyme systems gradually repair themselves during growth, a generally plausible idea of the retraining can be formed. The lags characteristic of the competing reaction systems vary in a rather random way from one subculture to another owing to the lack of control of the inoculum ages: hence the fluctuations in rate and the occasional appearance of the segmented curves (see "Chemical Kinetics of the Bacterial Cell," Oxford, 1946, p. 161).

FIG. 3.



Repair of damaged enzyme systems is thus a possible explanation of the retraining process. A single reverse mutation would not explain the quantitative picture.

On the other hand, a complex series of mutations which were reversed one by one at various stages of the training would give a good explanation of the very slow and erratic character of the phenomenon. Such an assumption, however, does not represent the most economical hypothesis. Nor does it explain the frequent relapses in the return of the mean generation time to the standard value. According to the hypothesis of spontaneous reverse mutation each stage of recovery (so long as no fresh exposure to the ultra-violet light occurred) should at least be permanent.

TABLE II.

Mean generation times during serial subculture of strain No. 14 *in the normal synthetic medium.*

Sub-culture no.	M.g.t. (mins.).	Sub-culture no.	M.g.t. (mins.).	Sub-culture no.	M.g.t. (mins.).	Sub-culture no.	M.g.t. (mins.).
1	45	19	41	36	37	53	38
2	45	20	39	37	44/30	54	37
3	44			38	36	55	36
4	49	21	38	39	39	56	32
5	43	22	42	40	37	57	36
6	45	23	38			58	36
7	40/52	24	38	41	35	59	35
8	37/51	25	37	42	35	60	36
9	38/43	26	37	43	39		
	35/43	27	37	44	33	61	35
		28	35	45	32	62	31
11	38	29	38	46	40	63	37
12	39/46	30	38	47	47	64	39
13	38			48	32	65	34
14	38/46	31	37	49	33	66	33
15	35/45	32	38	50	34	67	36
16	40	33	38			68	32
17	36	34	35	51	43	69	30
18	40	35	33	52	36	70	32

Where two figures are given a composite growth curve is indicated.

Mean values of the m.g.t. for the successive ranges of 10 sub-cultures:

No.	1—10	11—20	21—30	31—40	41—50	51—60	61—70
M.g.t. (mins.)	44	40	38	37	36	37	34

According to the hypothesis that damaged enzyme systems gradually repair themselves the fluctuations are natural. Growth is characterised by lag and by mean generation time. Lag is a function of age, and therefore if we have a makeshift metabolic route (used by the damaged cell) competing with a gradually more practicable route, the lags of the one or the other will vary according to the exact age of the culture when it is tested. The one or the other method of growth may, therefore, at intermediate stages be the one followed on any given occasion.

The chief difficulty about this view is to explain the extreme slowness of the retraining (so easily accounted for if a long wait for a favourable mutation is postulated). The explanation which the hypothesis can offer is as follows. The damaged cell can in fact grow by a makeshift metabolic route, but as long as this is functioning it by-passes processes in which the repair of the enzyme systems would occur through linking of function and reproduction of enzyme systems. Retraining occurs only when the makeshift mechanism lags long enough to allow the damaged normal mechanism to be utilised (however slowly) and so repair itself.

This view predicts an experimentally verifiable effect. If serial subcultures are carried out continuously without interruption the retraining should be slower than it is when the cultures are allowed to age considerably in each cycle. With mutant 14 retraining required 70 subcultures when transferred at 24-hour intervals, but 117 when subcultured at twice this frequency. Mutant No. 20 when subcultured daily showed a broken growth curve with mean generation times of 72/39 at the 6th subculture, while it showed a mean generation time of 30 minutes at the 6th subculture when transferred at intervals of three days. It seems reasonable to infer that when the conditions are such as to allow mechanisms with a long lag (impaired enzyme systems) to compete, the retraining process is favoured.

On the whole, therefore, we may conclude that, as far as the present set of experiments on the quantitative picture of the recovery phenomenon goes, the hypothesis of a direct retraining involves fewer difficulties and assumptions than the alternative.

PHYSICAL CHEMISTRY LABORATORY, OXFORD UNIVERSITY. [*Received, October 31st*, 1950.]

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262. *Induced and Other Variations in Bacterial Cultures. Part IV. Restoration of Normal Biochemical Reactions in Fermentative Mutants of* Bact. lactis aerogenes.

By A. C. R. DEAN and SIR CYRIL HINSHELWOOD.

The restoration of normal fermentative reactions in mutants of *Bact. lactis aerogenes* is subjected to a quantitative study in the light of theories of back mutation and of repair to damaged enzyme systems.

IT has been mentioned previously (Part II, *J.*, 1951, 1159) that, after the training to the normal growth rate, the biochemical reactions of the irradiated *Bact. lactis aerogenes* strains were normal. The manner in which the cells regain their ability to ferment various substrates should provide further evidence relevant to the question of mutation or adaptation. If a single reverse mutation is responsible for the recovery, all the lost functions should re-appear simultaneously, while with adaptation graded recovery is quite likely. Graded recovery would also occur if a whole series of minor mutations was involved, but in this case the individual biochemical characters should at least re-appear with full quantitative intensity (unless very special hypotheses about mutual influences of characters are invented).

Strain No. 14 was inoculated from broth into the asparagine–glutamic acid medium, and from the latter was serially sub-cultured in the synthetic medium twice daily until trained. Sugar fermentation tests were carried out at every fourth sub-culture, with the wide range of sugars described previously. Control experiments with a normal strain were set up with every experiment. A normal strain of *Bact. lactis aerogenes* ferments all the sugars, except D-arabinose, in 24 hours at 37°, the arabinose requiring 48 hours. The usual American practice (Prescott, Winslow, and McGrady, " Water Bacteriology," Wiley, New York, 1946, p. 202) allows 48 $\pm$ 3 hours as a time limit for the coliform group, and in order to ensure a wide margin of safety, the fermentation tests were kept for one week, and were read at daily intervals.

Over the first 68 sub-cultures the only difference in the results with increasing time of test was a tendency for an acid reaction to become alkaline, and hence only the results after one week were recorded. If an acid reaction was given at first, even if it subsequently became alkaline, it is reported as acid (Table I). From sub-culture 72 to 117 detailed results are necessary, and are shown in Table II.

TABLE I.

Fermentation reactions during serial sub-culture of strain No. 14 *in the normal synthetic medium. Results after one week.*

Sugar.	A/G †	Sub-cultures in normal synthetic medium.																	
		1	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68
D-Arabinose	—	A	—	—	—	—	A	A	—	A	—	—	A	—	—	A	A	—	—	—
Xylose	—	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Raffinose	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Glucose	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Mannose	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Galactose	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Sucrose	A	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	A	—	—	—
Maltose	A	—	A	—	A	A	A	—	—	A	A	A	A	A	—	A	A	A	—	—
Lactose	—	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	—	A	A
Cellobiose	A	A	A	A	A	A	A	A	A	A	A	A	A	A	—	—	—	A	—	—
Melibiose	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Inositol	—	A	A	A	—	—	A	A	A	—	—	A	A	—	—	A	A	—	—	—
Sorbitol	A	A	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Rhamnose	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
M.g.t.	—	—	51	48	46	48	55	$\frac{59}{47}$ *	40	$\frac{62}{40}$ *	51	43	$\frac{30}{46}$ *	38	$\frac{37}{41}$ *	$\frac{37}{41}$ *	44	42	42	$\frac{52}{33}$ *

* Composite growth curve. —, No acid, no gas.
A, Acid. † Asparagine-glutamic acid medium.

The recovery of the fermentative abilities is gradual, and for more than half of the training period acid was produced from some sugars whilst with others there was no reaction. Then the ability to produce gas was recovered gradually. It took place first with sucrose as the substrate (sub-culture No. 72); the amount produced was small, and 5 days' incubation was necessary. This property was then lost, and re-appeared at sub-culture No. 84, disappeared again, and was not apparent again until almost the end of training process. Meanwhile gas production appeared with mannose (sub-culture No. 80), xylose, maltose, lactose, and cellobiose (sub-culture No. 93), and with glucose (sub-culture No. 101), and in these instances the same fading and re-appearance took place.

It is interesting that glucose and xylose were the only substrates from which acid was produced in every test.

When sub-culture No. 117 was fully trained, acid and gas were produced from all the sugars, except arabinose, within 24 hours, and from arabinose within 48 hours. This is the behaviour of a normal strain of *Bact. lactis aerogenes*, and the re-trained strain retained this behaviour after storage for one month in broth. The effect of any variation in the media used is ruled out by the fact that control tests with a normal strain carried out concurrently with each set of sugar reactions always yielded acid and gas from all the sugars except arabinose in 24 hours, and from arabinose in 48 hours.

In seeking possible explanations for the behaviour encountered in these tests it is necessary to have a clear picture of the operations involved in the tests. They may be summarised as follows:

growth in synthetic medium ⟶ growth in peptone water ⟶ growth in peptone water in the presence of the various sugars

The first explanation to be considered is that of a single genetic mutation (reversion), *i.e.*, at some stage in the growth processes a normal organism is thrown off. If such a reversion had

Footnotes to Table II.

* 8 and 9 days same as 7 days. —, No acid, no gas. A, Acid, no gas.
$\frac{A}{sg}$, Acid, small volume of gas. AG, Acid, normal volume of gas.
† 6 days and 7 days same as 5 days.

TABLE II.

Fermentation reactions during serial sub-culture of strain No. 14 in the normal synthetic medium. Detailed results.

Sub-culture number in normal synthetic medium.

Sugar.	No. 72.							No. 76.							No. 80.							No. 84.						
D-Arabinose	—	—	—	—	—	—	—	—	—	—	A	A	—	—	—	—	—	—	A	A	—	—	—	—	—	—	—	—	—
Xylose	—	A	A	A	A	—	—	—	—	A	A	—	—	—	A	A	A	A	A	—	—	—	—	A	A	A	—	—	—
Raffinose	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Glucose	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	—	A	A	A	A	A	—	—	—
Mannose	A	A	A	A	A	A	A	A	A	A	A	A	A	A	—	—	A	A	A	A	A/sg	—	A	A	A	A/sg	A/sg	A/sg	—
Galactose	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	—	A	A	A	A	A	A	A	—
Sucrose	—	A	A	A	A/sg	A/sg	A/sg	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	A	A/sg	A/sg	A/sg	—
Maltose	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	A	A	A	A	A	—	—	—
Lactose	—	A	A	A	—	—	—	—	A	A	A	A	A	A	A	A	A	A	A	—	—	A	A	A	A	A	A	A	—
Cellobiose	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Melibiose	—	—	—	—	—	—	—	A	A	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Inositol	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Sorbitol	—	—	—	—	—	—	—	—	A	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Rhamnose	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Time (days)	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7*	1	2	3	4	5	6	7	
M.g.t. (mins.)				52							52							42							46				

Sugar.	No. 89.							No. 93.							No. 97.							No. 101.						
D-Arabinose	—	—	—	—	—	—	—	—	A	A	A	A	A	A	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Xylose	—	A	A	A	A	A	—	A	A	A/sg	A/sg	A/sg	A/sg	—/sg	—	—	A	—	—	—	—	—	—	A	A	A	A	—	—
Raffinose	A	A	A	A	A	A	A	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Glucose	A	A	A	A	A	A	—	A	A	A	A	A	A	—	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A/sg
Mannose	—	—	—	—	—	—	—	—	A	—	—	—	—	—	—	—	—	—	—	—	—	A	A	A	A	A	A	A	A/sg
Galactose	A	A	A	A	A	—	A	—	A	A	A	A	A	A	—	—	—	—	—	—	—	A	A	A	A	A	A	A	—
Sucrose	—	—	—	—	—	A	A	—	—	—	—	—	—	—	—	—	—	—	—	—	—	A	A	A	A	A	A	A	—
Maltose	—	—	—	—	—	—	—	A	AG	AG	AG	AG	AG	AG	—	—	—	—	—	—	—	—	A	A	A	—	—	—	—
Lactose	—	A	—	—	—	—	—	—	A	A/sg	A/sg	A/sg	A/sg	A/sg	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cellobiose	—	—	—	—	—	—	—	A	AG	AG	AG	AG	AG	AG	—	—	—	—	—	—	—	A	A	A	A	A	A	A	A/sg
Melibiose	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Inositol	—	—	—	—	—	—	—	—	A	A	A	A	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Sorbitol	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Rhamnose	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	A	—	—	—	—
Time (days)	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7*	
M.g.t. (mins.)				33/54							36							44							41				

Sugar.	No. 105.							No. 109.					No. 117.		Normal strain.	
D-Arabinose	—	—	—	—	—	—	—	—	—	—	—	—	—	AG	—	AG
Xylose	—	A	A	A	A	A	A	A	A	A	A	A/sg	AG	—	AG	—
Raffinose	—	—	—	—	—	—	—	—	—	—	—	—	AG	—	AG	—
Glucose	A	A	A	A	A	A	A/sg	A	A	A	A	A/sg	AG	—	AG	—
Mannose	—	A	A	A	A	A	A/sg	A	A	A	A	A/sg	AG	—	AG	—
Galactose	A	A	A	A	A	A	—	A	A	A	A	A/sg	AG	—	AG	—
Sucrose	—	A	A	A	A	A	A/sg	A	A	A	A	A/sg	AG	—	AG	—
Maltose	—	A	A	A	A	A	—	A	A	A	A	A/sg	AG	—	AG	—
Lactose	—	A	A	A	A	A	—	A	A	A	A	A/sg	AG	—	AG	—
Cellobiose	—	A	A	A	A	A	—	A	A	A	A	A/sg	AG	—	AG	—
Melibiose	—	—	—	—	—	—	—	—	—	—	—	—	AG	—	AG	—
Inositol	—	—	—	—	—	—	—	—	—	—	—	—	AG	—	AG	—
Sorbitol	—	—	—	—	—	—	—	—	—	—	—	—	AG	—	AG	—
Rhamnose	—	—	—	—	—	—	—	—	—	—	—	—	AG	—	AG	—
Time (days)	1	2	3	4	5	6	7*	1	2	3	4	5†	1	2	1	2
M.g.t. (mins.)				42						38			31		32	

4 G

Footnotes at foot of opposite page.

taken place during the serial sub-cultures in the synthetic medium, the mean generation time and fermentation reactions in all the succeeding sub-cultures would have been normal. This could only have taken place between sub-cultures 109 and 117, and is very unlikely in view of the gradual recovery of the sugar reactions. The possibility that reversion may have taken place during the actual sugar tests themselves must also be considered. With any one sugar four possible results must be explained, *viz.*, no reaction, acid, acid with a small volume of gas, and the normal reaction. It would be necessary to postulate one mutation resulting in the ability to produce acid, *i.e.*, resulting in the appearance of the enzyme or enzymes necessary for transforming the sugar into hexose phosphate. Since glucose was degraded to acid in every test, it may be assumed that the enzymes necessary for the conversion of hexose phosphate into acid are already present in the cell. With arabinose, rhamnose, sorbitol, and inositol, the route may not be *via* hexose phosphate; in these cases the assumption would be that the mutation results in the appearance of an enzyme or enzymes necessary for the transformation of each substrate into acid. Another mutation resulting in the formation of gas would also need to be assumed, and it is difficult to see how this would account for the production of the small volume of gas obtained during the training process, unless the mutation took place when almost all the nitrogen in the culture medium had been used up, limiting the amount of enzyme that could be formed.

Further difficulties are encountered with the simple form of the mutation hypothesis when it is considered that the mutation resulting in acid production would have to take place very frequently, whilst that resulting in the production of gas would be of much rarer occurrence. In fact, the latter mutation would not have occurred at all during the first half of the training period, and fairly infrequently during the second part of the process, until the penultimate series of tests, in which the frequency would have increased greatly. In this penultimate stage, two types of response only were obtained. With 6 sugars no reaction took place, *i.e.*, no mutation could have occurred; from the remaining 8 sugars, acid and a small amount of gas were produced, *i.e.*, both mutations must have taken place together, and in all of them the mutation responsible for gas production must have taken place when almost all the nitrogen in the culture medium had been used up. Such a combination of events seems improbable.

The gradual recovery of fermentative abilities during training tends, by itself, to favour the alternative theory of adaptation as an explanation for the observed behaviour. This would postulate that, as the strain is serially sub-cultured in the normal synthetic medium, damaged enzyme systems are repaired and expanded until the growth rate and biochemical properties become normal. Incidentally, the postulate would include the hypothesis of Sevag (*Adv. in Enzymology*, 1946, **6**, 83), who believes that in some cases the recovery of irradiated cells can be explained on the basis of the return to the native state of certain proteins, which have been denatured, deformed, or distorted by the irradiation.

Whatever might be postulated about multiple mutations to explain graded reversion, one fact which would remain difficult to account for is the sort of time relation exemplified by the behaviour at sub-cultures 105, 109, and 117 (Table II). With mannose, for example, at 105 small amounts of gas appear after 7 days of test, at 109 they are evident after 5 days only, while at 117 not only does gas appear in full amount, but within one day. This certainly has the appearance of a quantitative development rather than of a qualitative discontinuity in character.

Although the conditions for carrying out the sugar tests were standardized as far as possible, it is evident that the cells from the various sub-cultures in the normal synthetic medium would not all be of the same biological age, and hence the enzymes would have decayed to varying degrees. This would result in different lags in the peptone water, and since the cells were inoculated into the sugar media after a definite time in the former, the properties of the various enzymes in the cells used in the different experiments would not be the same. Such behaviour would explain the production of acid in one experiment and its absence in subsequent experiments with the same sugar. Since the cells were serially sub-cultured in the glucose medium, it is not surprising that acid was invariably produced from it in the sugar tests. The enzymes in the cells would be better adapted to glucose than to any other sugar, and it is believed that in the aerobic and anaerobic disruption of glucose the same enzymes are concerned with part of the process, namely the conversion of glucose into pyruvic acid. Sevag (*ibid.*, p. 77) has suggested that hexokinase is responsible for converting glucose, mannose, and galactose into hexose phosphates in yeasts. It is interesting to note that acid was produced from galactose in all but one test, and from mannose in all but two tests. Probably other factors are also involved besides hexokinase in the fermentation of these two sugars.

Genetic Recombination.—Genetic recombination has been stated to occur by Tatum and

Lederberg (*J. Bact.*, 1947, **53**, 673) in a strain of *Bact. coli*. A synthetic agar medium was used as a selective sieve to isolate occasional recombinants which appeared in mixed cultures of complementary biochemical mutants. Later experiments introduced other factors, such as fermentation and virus-resistance, and these factors were found to segregate in a manner which suggested linkage.

A crossing experiment was carried out with two strains with abnormal biochemical characters One of them, No. 14, had been isolated by ultra-violet irradiation of *Bact. lactis aerogenes*, and was "sucrose-acid (no gas)," and "xylose-negative"; the other, F 23/5, isolated from an experiment with Fenton's reagent, was "sucrose-negative" and "xylose-acid (no gas)." 10 Ml. of broth were inoculated with one loopful of each of the strains and incubated for 3 weeks, after which a dilution was plated out on a complete agar, and 10 colonies were selected and tested for sucrose and xylose fermentation. Controls were put on at the same time for both of the strains. Results appear in Table III.

TABLE III.

"Crossing" experiment between strain No. 14 and strain F 23/5.

	No. 14.		F 23/5.		Cross.			No. 14.		F 23/5.		Cross	
	Suc.	Xyl.	Suc.	Xyl.	Suc.	Xyl.		Suc.	Xyl.	Suc.	Xyl.	Suc.	Xyl.
24 *Hours.*							48 *Hours.*						
1	A	—	—	—	—	—	1	A	—	—	—	—	A
2	A	—	—	—	—	—	2	A	—	—	A	—	A
3	A	—	—	—	—	—	3	A	—	—	—	—	A
4	A	—	A	—	—	—	4	A	—	A	—	—	A
5	A	—	—	—	A	—	5	A	—	A	—	*A*	*A*
6	A	—	—	—	—	A	6	A	—	—	A	—	A
7	A	—	—	—	A	—	7	A	—	—	A	*A*	*A*
8	A	—	—	—	—	A	8	A	—	—	—	—	A
9	A	—	A	—	—	A	9	A	—	A	—	—	A
10	A	—	—	—	—	A	10	A	—	—	—	—	A
72 *Hours.*													
1	A	—	—	A •	—	A	*Parent cultures.*						
2	A	—	—	A	—	A					Sucrose.	Xylose	
3	A	—	*A* •	*A*	—	A	No. 14				A	—	
4	A	—	*A*	*A*	—	A	F 23/5				—	A	
5	A	—	*A*	*A*	*A*	*A*							
6	A	—	—	A	—	A	• Weak reaction.						
7	A	—	—	A	*A*	*A*							
8	A	—	—	A	—	A							
9	A	—	*A*	*A* •	—	A	Note.—*A* (italic) indicates result of crossing.						
10	A	—	—	A	—	A							

Even if rare cell conjugations leading to recombinations of genes occurred, it is obvious that the chance of isolating the relevant progeny might be negligibly small in the present case where no screening process is available. Nevertheless the sugar tests actually gave results which might have been formally interpreted as indicating a crossing of the two strains. Nos. 5 and 7 at 48 hours show the combination AA instead of A– or –A. But at 72 hours four of the controls had also developed the characters of crosses, so that the apparent evidence of recombination is revealed as completely illusory. One point which may perhaps be emphasised here is that had the test been cut off at 48 hours apparently controlled evidence of crossing would have been reported. The importance of the quantitative factor in test times is here revealed once again. It is not always observed, though Lindegren emphasises it throughout his book ("The Yeast Cell," Educational Publ., Saint Louis, 1949).

One of the authors (A. C. R. D.) expresses his appreciation to the Carnegie Trust for the Universities of Scotland for the award of a Senior Scholarship.

PHYSICAL CHEMISTRY LABORATORY, OXFORD UNIVERSITY. [*Received, October 31st*, 1950.]

263. *Melting-point and X-Ray Data for 2 : 4-Dinitrophenylhydrazones of n-Aliphatic Aldehydes.*

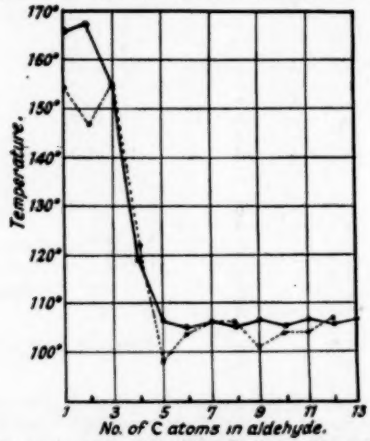
By T. Malkin and T. C. Tranter.

The melting points of 2 : 4-dinitrophenylhydrazones of *n*-aliphatic aldehydes from valeraldehyde upwards, lie within too narrow a range to afford a reliable means of identification. Long *X*-ray spacings are found to be suitable for this purpose.

The value of 2 : 4-dinitrophenylhydrazine as a reagent for carbonyl compounds is well known (cf. Wild, "Characterisation of Organic Compounds," Cambridge Univ. Press, p. 112) but, as Campbell has pointed out (*Analyst*, 1936, **61**, 391), care is required in its use, owing to the many discrepancies in the recorded melting points of its derivatives. Although Campbell revised many of the latter, he did not do so for the derivatives of *n*-aliphatic aldehydes, the melting points of which fall on an unusually irregular curve (Fig. 1). In view, therefore, of the value

Fig. 1.

M. p.s of 2 : 4-dinitrophenylhydrazones of n-aliphatic aldehydes.



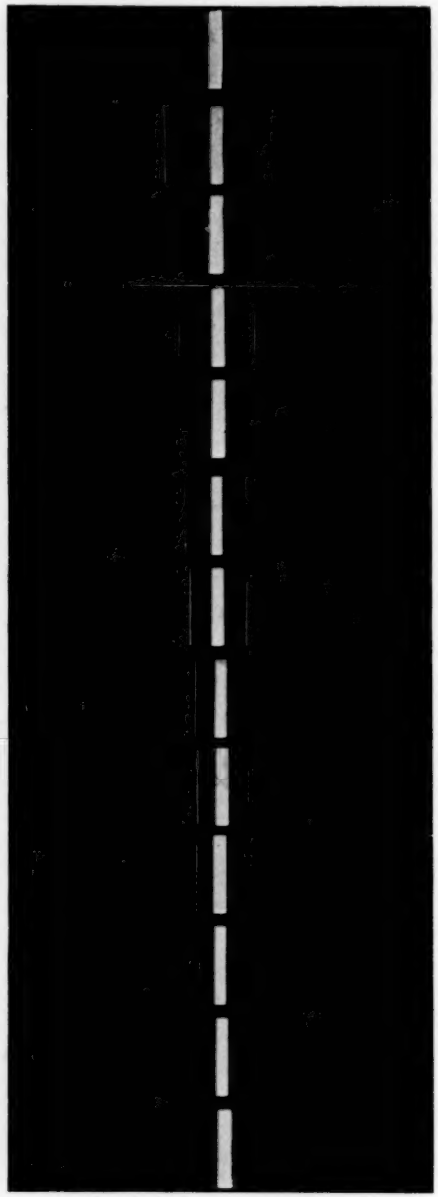
Discontinuous lines : m. p.s reported by Allen, J. Amer. Chem. Soc., 1930, **52**, 2955.

of a ready means of identification of these aldehydes, for example, in constitutional studies of unsaturated fatty acids, we have revised the melting points, using authentic aldehydes (Fig. 1; Table). These now show a more normal behaviour, but unfortunately the higher members

No. of C atoms in aldehyde.	M. p.	Long spacings, A.	Side spacings, A.								
1	166°	7·33, 10·38	3·09	—	3·48	3·64	—	—	—	—	—
2	167·5	9·40	—	3·25v	3·4	3·63	—	—	—	—	—
3	155	10·95, 9·64	—	3·26	3·42	—	—	—	—	4·40	4·74
4	119	13·5	—	3·27	3·37m	—	3·82	—	—	4·41m	—
5	106	15·08	—	3·25	—	3·66	3·78	—	—	—	—
6	105	16·34	—	3·25	—	—	3·72	—	4·15m	4·5m	—
7	106	17·78	3·21m	3·31	—	—	3·76	4·08m	4·17m	4·45	4·63
8	105·5	19·15	—	3·28	—	—	3·74	—	4·22	4·58	—
9	106·5	19·6	—	3·26	—	3·68	—	3·96m	—	—	4·72
10	106	21·12	—	3·26	—	3·69	—	3·95m	—	—	4·72
11	106·5	22·38	—	3·28	—	3·71	—	3·96	—	—	4·75
12	106	23·95	—	3·25	—	3·65	—	3·91	—	—	4·73
13	106·5	25·4	—	3·29	—	3·69	—	3·99	—	—	4·77

Only the strong spacings are recorded : m = moderately strong; v = very strong.

X-*Ray long spacings of the* 2 : 4-*dinitrophenylhydrazones of the normal aliphatic aldehydes.*



Formaldehyde.

Acetaldehyde.

Propaldehyde.

n-*Butaldehyde.*

n-*Valeraldehyde.*

n-*Hexanal.*

n-*Heptanal.*

n-*Octanal.*

n-*Nonanal.*

n-*Decanal.*

n-*Undecanal.*

n-*Dodecanal.*

n-*Tridecanal.*

[*To face p.* 1179.

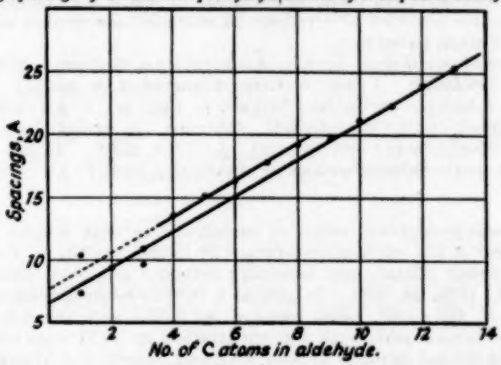
(from C_3 to C_{13} aldehydes) melt over a range of only 1·5°, and are thus of little value for purposes of identification. As, however, these derivatives have the advantage over most others in ease of preparation, we have, as an alternative method of identification, determined their *X*-ray spacings (Table; Fig. 2; and Plate). These fall on two parallel straight lines with a break indicating a slight change in structure between C_8 and C_9 (Fig. 2). Except for the last two, which differ by 0·45 A., the difference in spacings between homologues is ≏1·4 A., which is well beyond any likely experimental error. Even with C_8 and C_9, where an intermediate value might give rise to doubt, the two are readily distinguished by the photographs (cf. differences in intensity of the lines, and the double line at the third order on C_9; see Plate), and should doubt still exist, the side spacings distinguish them decisively.

Experimental.

The dinitrophenylhydrazones were made by Brady's method (sulphuric acid and ethyl alcohol) (*J.*, 1931, 756), and crystallised from methyl alcohol. In agreement with Campbell (*loc. cit.*), we found benzene an unsatisfactory solvent, m. p.s being many degrees low after several crystallisations.

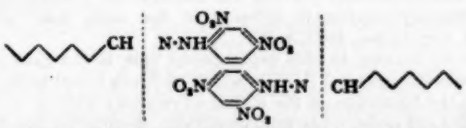
Fig. 2.

Long spacings of 2 : 4-*dinitrophenylhydrazones of* n-*aliphatic aldehydes.*



X-*Ray Investigation.*—A Müller spectrograph was used with a Metalix *X*-ray tube (Cu-K_α, λ = 1·54 A.) running at ≏10 ma., distance of specimen from film, 6 cm. Long spacings were obtained from pressed layers, and side spacings from rods (see *J.*, 1936, 1631) or from loosely packed capillaries of goldbeater's skin. Exposures of ½ hour for rods, or of ½ hour each side of centre for layers, were adequate.

The increment per carbon atom of 1·4 A. indicates a structure of layers of double molecules, tilted at an angle of about 34° to the reflecting planes (an increment of 1·26 A. per carbon atom being assumed for a vertical zig-zag hydrocarbon chain). The intercepts at 0 carbon atom (Fig. 2) of 6·5 A. and 7·6 A., respectively, for the two forms, would suggest an almost complete overlap of the aromatic heads of the double molecule, *viz.*



This would not be inconsistent with the spacing of 5·89 A. found for 2 : 4-dinitrophenylhydrazine itself, which might well crystallise in the head-to-tail arrangement indicated above, between the dotted lines.

During our investigation, we confirmed the results of Miss F. O. Bell (*Biochem. J.*, 1941, **35**, 312), who gave *X*-ray evidence for the dimorphism of the 2 : 4-dinitrophenylhydrazone of acetaldehyde, noted earlier by other workers (Bryant, *J. Amer. Chem. Soc.*, 1933, **55**, 3201; Ingold, Pritchard, and Smith, *J.*, 1934, 86), and it is hoped shortly to publish details of the structures of the two forms.

Department of Organic Chemistry,
The University, Bristol.

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264. *Anhydrides of Polyhydric Alcohols. Part XV. The Reactions of Sodium Iodide and Lithium Chloride with Dimethanesulphonyl and Ditoluene-p-sulphonyl Derivatives of the* 1 : 4-3 : 6-*Dianhydrides of* D-*Mannitol,* D-*Sorbitol, and* L-*Iditol.*

By L. F. Wiggins and D. J. C. Wood.

The reactivity of the sulphonyl groups in methanesulphonyl and toluene-*p*-sulphonyl derivatives of the dianhydrides of the epimeric series D-mannitol, D-sorbitol, and L-iditol has been shown to be related to the stereochemistry of the hexitols. In the case of mannitol derivatives both groups are replaced by iodine on treatment with sodium iodide or by chlorine on treatment with lithium chloride. In the case of the corresponding sorbitol derivatives, which differ from the mannitol compounds only by the configuration at $C_{(2)}$, only one sulphonic acid residue is replaced by either iodine or chlorine. When analogous derivatives of dianhydro-L-iditol, in which the configurations of $C_{(2)}$ and $C_{(5)}$ are reversed with respect to mannitol, are treated similarly no reaction occurs in either case.

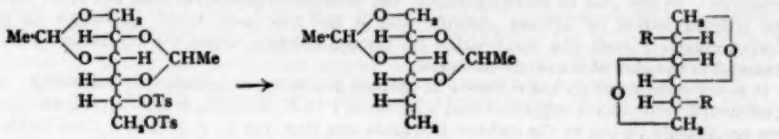
The ease of reaction of the three dianhydrides with thionyl chloride shows a similar gradation. 1 : 4-3 : 6-Dianhydromannitol is readily converted into the 2 : 5-dichloro-derivative (Wiggins, *J.*, 1945, 4); 1 : 4-3 : 6-dianhydrosorbitol gives, with considerable difficulty, a monochloro-derivative (Overend, Montgomery, and Wiggins, *J.*, 1948, 2201). It has not been possible to isolate chlorine-containing derivatives from 1 : 4-3 : 6-dianhydro-L-iditol.

Treatment of toluene-*p*-sulphonic esters of carbohydrates with sodium iodide in acetone, leading to replacement of the sulphonyloxy-groups by iodine, constitutes a well-known method of distinguishing between primary and secondary hydroxyl groups (Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366). In general a toluene-*p*-sulphonyloxy-group attached to CH_2 reacts readily at 100—105°, being replaced by iodine with simultaneous formation of sodium toluene-*p*-sulphonate, while such a group attached to >CH· does not react. Methanesulphonyl derivatives behave similarly (Foster, Overend, Stacey, and Wiggins, *J.*, 1949, 2542). The degree to which replacement occurs varies with different compounds, being influenced by neighbouring groups in the molecule.

Exceptions to Oldham and Rutherford's rule have however been reported. Thus when vicinal primary and secondary toluene-*p*-sulphonyloxy-groups are present, both are removed; two equivalents of sodium toluene-*p*-sulphonate are produced but, instead of a di-iodo-derivative, an unsaturated compound results. Thus 1 : 3-2 : 4-diethylidene 5 : 6-ditoluene-*p*-sulphonyl sorbitol (I) gives 1 : 3-2 : 4-diethylidene 5 : 6-sorbitoleen (II) (Bladon and Owen, *J.*, 1950, 598). Similarly, all the toluene-*p*-sulphonyloxy-residues in glycerol tritoluene-*p*-sulphonate are removed by sodium iodide treatment (Levene and Mehltretter, *Enzymologia*, 1937, **4**, ii, 232), and erythritol tetratoluene-*p*-sulphonate behaves in the same way, furnishing butadiene (Tipson and Cretcher, *J. Org. Chem.*, 1943, **8**, 95).

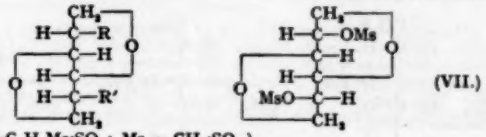
Notable among the exceptions to this replacement rule is the case of 2 : 5-ditoluene-*p*-sulphonyl 1 : 4-3 : 6-dianhydromannitol (III), in which both sulphonyl groups are quantitatively replaced by iodine with the formation of the di-iodo-compound (IV; R = I) when the sodium iodide treatment is carried out under quite mild conditions, despite the fact that both sulphonyloxy-residues are known with certainty to be secondary (Hockett *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 930). It has now been found that the reaction (III) ⟶ (IV) is only one case of a more general peculiarity of sulphonyl derivatives of 1 : 4-3 : 6-dianhydrohexitols. 2 : 5-Dimethanesulphonyl 1 : 4-3 : 6-dianhydromannitol (V) reacted readily with sodium iodide in acetone to give the same 2 : 5-di-iodo-1 : 4-3 : 6-dianhydro-2 : 5-dideoxymannitol (IV; R = I) as is obtained from the corresponding toluene-*p*-sulphonyl derivative (III). Dimethanesulphonyl dianhydrosorbitol (VI) also underwent reaction with sodium iodide, but in this case only one methanesulphonyl group was replaced, giving a methanesulphonyl monoiodo-1 : 4-3 : 6-dianhydrodeoxysorbitol in 27% yield; this compound is probably (VIII; R′ = I). 2 : 5-Dimethanesulphonyl 1 : 4-3 : 6-dianhydro-L-iditol (VII) was, however, almost completely

unaffected by sodium iodide treatment: the yield of sodium methanesulphonate was only 4·1%, and a 90% recovery of the dimethanesulphonate was obtained.



(I.) (II.) (III; R = OTs.) (IV; R = Cl or I.) (V; R = OMs.)

(VI; R = R′ = OMs.)
(VIII; R = OMs, R′ = Cl or I.)
(IX; R = OH, R′ = Cl.)



(VII.)

(Ts = *p*-$C_6H_4Me\cdot SO_2$; Ms = $CH_3\cdot SO_2$.)

Clarke and Owen (*J.*, 1949, 315) have shown that the monomethanesulphonyl and monotoluene-*p*-sulphonyl derivatives of *cyclo*hexane-1 : 2-diol readily react with sodium iodide in acetone and also with lithium chloride in alcohol; in the latter case the sulphonyloxy-group is replaced by chlorine. This suggested that the action of lithium chloride on dimethanesulphonyl dianhydrohexitols might be studied, and it has been found that reaction does take place, although rather more drastic conditions, namely, heating at 150° for 48 hours, are necessary to effect it. The chlorine-exchange reaction with the three isomeric dimethanesulphonyl compounds follows exactly the same course as iodine-exchange. 2 : 5-Dimethanesulphonyl 1 : 4-3 : 6-dianhydromannitol (V) yielded 2 : 5-dichloro-1 : 4-3 : 6-dianhydro-2 : 5-dideoxymannitol (IV; R = Cl), identical with that prepared by Wiggins (*J.*, 1945, 4) by direct chlorination of dianhydromannitol. Dimethanesulphonyl dianhydrosorbitol (VI) gave under the same conditions a methanesulphonyl monochlorodianhydrodeoxysorbitol (VIII; R′ = Cl). Hydrolysis of this with sodium hydroxide led to the formation of the monochlorodianhydrodeoxysorbitol reported by Overend, Montgomery, and Wiggins (*J.*, 1948, 2201) as a product of the action of thionyl chloride on 1 : 4-3 : 6-dianhydrosorbitol. From these facts it is certain that the monochloro-compound must be either 2- or 5-chloro-1 : 4-3 : 6-dianhydro-2(5)-deoxysorbitol; it is not possible as yet to decide definitely which of these alternatives is correct, but there is no reason to dispute the argument put forward by Overend, Montgomery, and Wiggins that it is probably the 5-chloro-compound (IX).

In an attempt to replace both methanesulphonyloxy-residues in dimethanesulphonyl 1 : 4-3 : 6-dianhydrosorbitol by chlorine, the compound was heated with lithium chloride in alcohol–acetone at a higher temperature. The liquid product which was obtained in small yield was free from sulphur, but ultimate analysis indicated that it contained only one chlorine atom; in addition it was found to be unsaturated. It is tentatively formulated as a monochlorodianhydrodeoxysorbitoleen.

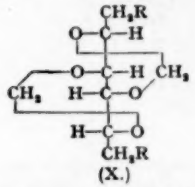
The action of lithium chloride on ditoluene-*p*-sulphonyl dianhydrosorbitol under the normal conditions was found, as expected, to give the toluene-*p*-sulphonyl derivative of the monochlorodianhydrodeoxyhexitol of Overend, Montgomery, and Wiggins, but in lower yield than that in which the corresponding methanesulphonyl compound was obtained.

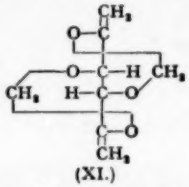
Interaction of 2 : 5-dimethanesulphonyl 1 : 4-3 : 6-dianhydro-L-iditol (VII) and lithium chloride did not lead to any definite results. After treatment at 150° the starting material was recovered in high yield, no other product being isolated; at 180° only a black tar was obtained.

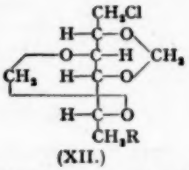
Thus, a considerable difference exists between the 1 : 4-3 : 6-dianhydro-derivatives of mannitol, sorbitol, and iditol regarding the reactivity of substituent sulphonyl groups at positions 2 and 5. The observed behaviour is closely paralleled by the results of the earlier attempts to introduce chlorine atoms directly into the dianhydrohexitol molecule by the action of thionyl chloride in pyridine. The dimethanesulphonate of the mannitol dianhydride reacts readily with replacement of both sulphonyloxy-groups by halogen, while the action of thionyl chloride on the dianhydride easily affords the same 2 : 5-dichloro-derivative. With dianhydro-

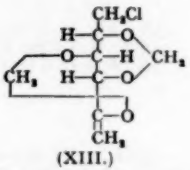
sorbitol, on the other hand, only one sulphonyloxy-group is replaced by halogen, and the action of thionyl chloride directly on the dianhydride results in the formation of a monochloro-derivative. In the case of dianhydroiditol, the dimethanesulphonate does not react smoothly with sodium iodide or lithium chloride and it has now been found impossible to obtain chloro-derivatives from the dianhydride by thionyl chloride under the conditions which are successful in the case of dianhydromannitol.

It is not possible, from the evidence at present available, to explain this behaviour. Other experimental results have suggested that whereas in 1 : 4-3 : 6-dianhydromannitol both anhydro-rings are equally stable, in the sorbitol isomeride one ring (the 1 : 4) is rather more stable than the other; these facts bear some similarity to the observed variations in reactivity of the anhydrides in substitution reactions, but no theoretical basis for a connection between these effects is as yet apparent. Of allied interest are some observations on the reactivity of halogen


(X.)


(XI.)


(XII.)


(XIII.)

substituents attached to the terminal carbon atoms of various derivatives of mannitol and sorbitol. 2 : 4-3 : 5-Dimethylene 1 : 6-dichloro-1 : 6-dideoxymannitol (X; R = Cl) is known to react readily with sodium or with alcoholic potash to yield "2 : 4-3 : 5-dimethylene 1 : 6-dideoxy-1 : 2-5 : 6-mannitoldiene" (XI) (Micheel, *Annalen*, 1932, **496**, 77; Haworth, Heath, and Wiggins, *J.*, 1944, 155) and with sodium iodide in acetone to give 2 : 4-3 : 5-dimethylene 1 : 6-di-iodo-1 : 6-dideoxymannitol (X; R = I) (Micheel, *loc. cit.*). The reaction of 2 : 4-3 : 5-dimethylene 1 : 6-dichloro-1 : 6-dideoxysorbitol (XII; R = Cl) (Haworth and Wiggins, *J.*, 1944, 58) with sodium was found to involve only one of the terminal carbon atoms, affording probably 2 : 4-3 : 5-dimethylene 1-chloro-1 : 6-dideoxy-5 : 6-sorbitoleen (XIII); a similar effect accompanied the reaction of the same dichloro-compound with sodium iodide, leading to the replacement of only one chlorine atom by iodine with the probable formation of 2 : 4-3 : 5-dimethylene 1-chloro-6-iodo-1 : 6-dideoxysorbitol (XII; R = I).

The structures assigned above to the two sorbitol derivatives are supported by work of Ness, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1944, **66**, 1901) on the action of sodium iodide in acetone on 2 : 4-3 : 5-dimethylene 1 : 6-ditoluene-*p*-sulphonyl sorbitol. These authors supplied conclusive evidence that the product of this reaction was 2 : 4-3 : 5-dimethylene 1-toluene-*p*-sulphonyl 6-iodo-6-deoxysorbitol, which demonstrates that it is $C_{(1)}$ which is unreactive in this case; it is reasonable to suppose that the same effect obtains with the chloro-derivatives discussed above. From purely theoretical considerations the same conclusion may be reached; the only difference between the mannitol and the sorbitol molecule lies in the configuration at $C_{(2)}$, and therefore it is probable that this end of the molecule is responsible for the difference in chemical behaviour of analogous mannitol and sorbitol derivatives. By extending this argument to L-iditol derivatives, in which the configuration of both $C_{(2)}$ and $C_{(5)}$ are reversed with respect to mannitol, it might be expected that both ends of the iditol chain would be unreactive in the circumstances under discussion and this appears in fact to be the case.

The replacement of methanesulphonyloxy-, toluene-*p*-sulphonyloxy-, or hydroxyl groups in dianhydrohexitol derivatives by iodine or chlorine atoms may of course lead to Walden inversion. We have assumed at this stage of the research, that no such inversion takes place and have named the compounds obtained according to the parent hexitol. We wish to make it clear, however, that the question whether or not configurational changes occur is not yet settled.

Experimental.

Action of Sodium Iodide on 2 : 5-*Dimethanesulphonyl* 1 : 4-3 : 6-*Dianhydromannitol.*—The dimethanesulphonate (10 g.) (Montgomery and Wiggins, *J.*, 1948, 2204) was heated in dry acetone with sodium iodide (30 g.) at 110° for 18 hours. The precipitate of sodium methanesulphonate was removed by filtration and the filtrate evaporated to dryness. The residue was extracted with a mixture of chloroform and water, and the chloroform layer separated, washed with dilute sodium thiosulphate solution and with water, dried ($MgSO_4$), and evaporated. Recrystallisation of the residue (7·5 g.) from alcohol gave 2 : 5-di-iodo-1 : 4-3 : 6-dianhydro-2 : 5-dideoxymannitol, m. p. 61—63°, $[\alpha]_D^{19}$ +107·9° (*c*, 1·97 in chloroform).

(Found : C, 19·8; H, 2·2. Calc. for $C_6H_8O_4I_2$: C, 19·7; H, 2·2%). Some difficulty was experienced in obtaining a product of well-defined m. p. Hockett *et al.* (*loc. cit.*) give m. p. 61—62°; Brigl and Grüner (*Ber.*, 1934, **67**, 1582) give m. p. 60—70°, $[\alpha]_D$ +101·4°.

Action of Sodium Iodide on 2 : 5-*Dimethanesulphonyl* 1 : 4-3 : 6-*Dianhydrosorbitol.*—The dimethanesulphonate (20 g.) (Bashford and Wiggins, *J.*, 1948, 299) was heated in dry acetone with sodium iodide (30 g.) at 125° for 12 hours. After removal of the sodium methanesulphonate the solution was evaporated to dryness and the product isolated as described above. *Methanesulphonyl monoiodo*-1 : 4-3 : 6-*dianhydrodeoxysorbitol* was obtained and, recrystallised from hot water, formed fine needles (6 g., 25%), m. p. 104—105°, $[\alpha]_D^{20}$ +74·2° (*c*, 2·42 in chloroform) (Found : C, 25·4; H, 3·4. $C_7H_{11}O_4IS$ requires C, 25·1; H, 3·3%).

Action of Sodium Iodide on 2 : 5-*Dimethanesulphonyl* 1 : 4-3 : 6-*Dianhydro*-L-*iditol.*—Dimethanesulphonyl dianhydroiditol (0·5 g.) (Wiggins, *J.*, 1947, 1403) was heated with sodium iodide (0·75 g.) in dry acetone (15 c.c.) at 110—120° for 8 hours. The solution was filtered hot to prevent crystallisation of the unchanged ester; the yield of sodium methanesulphonate was 0·016 g. (4·1%). On evaporation the filtrate gave the unchanged starting material (0·45 g., 90% recovery).

Action of Lithium Chloride on 2 : 5-*Dimethanesulphonyl* 1 : 4-3 : 6-*Dianhydromannitol.*—The dimethanesulphonyl compound (0·85 g.) was heated with anhydrous lithium chloride (0·55 g.), absolute alcohol (10 c.c.), and dry acetone (10 c.c.) at 150° for 48 hours. The solution was evaporated to dryness and extracted with water; the insoluble residue, recrystallised from alcohol, furnished long needles of 2 : 5-dichloro-1 : 4-3 : 6-dianhydro-2 : 5-dideoxymannitol (0·25 g., 49%), m. p. 63—64°, $[\alpha]_D^{20}$ +99·0° (*c*, 0·62 in chloroform). The m. p. was not depressed on admixture with an authentic specimen prepared by Wiggins's method (*loc. cit.*).

Action of Lithium Chloride on 2 : 5-*Dimethanesulphonyl* 1 : 4-3 : 6-*Dianhydrosorbitol.*—(i) Dimethanesulphonyl dianhydrosorbitol (0·85 g.) was treated with lithium chloride in alcohol–acetone as in the preceding experiment. The product, isolated as before, recrystallised from alcohol in long stout needles (0·45 g., 66%), m. p. 115—116°, $[\alpha]_D^{20}$ +71·6° (*c*, 0·53 in chloroform). It was *methanesulphonyl monochloro*-1 : 4-3 : 6-*dianhydrodeoxysorbitol* (Found : C, 35·1; H, 4·4; Cl, 15·7; S, 14·1. $C_7H_{11}O_4ClS$ requires C, 34·6; H, 4·5; Cl, 14·7; S, 13·2%). The m. p. was undepressed on admixture with the methanesulphonyl derivative prepared from the monochlorodianhydrodeoxysorbitol, m. p. 63—64°, described by Overend, Montgomery, and Wiggins (*loc. cit.*).

(ii) Dimethanesulphonyl dianhydrosorbitol (5·0 g.) was heated with anhydrous lithium chloride (3·2 g.), absolute alcohol (60 c.c.), and dry acetone (30 c.c.) in an autoclave at 180—190° for 48 hours. The solution was evaporated to dryness and the residue extracted with a mixture of chloroform and water. The chloroform layer was washed with water, dried ($MgSO_4$), and evaporated to a black syrup (3·0 g.). Distillation of the latter under reduced pressure gave a mobile liquid (0·4 g.), b. p. (bath-temp.) 145—150°/15 mm., n_D^{16} 1·5009, $[\alpha]_D^{20}$ +53·3° (*c*, 1·26 in chloroform). This was almost colourless when first collected but rapidly darkened on exposure to the air. It contained chlorine but no sulphur; it immediately decolorised a solution of bromine in carbon tetrachloride. The compound is tentatively described as a monochlorodianhydrodeoxysorbitoleen (Found : Cl, 26·0. Calc. for $C_6H_7O_4Cl$: Cl, 24·2%).

Hydrolysis of Methanesulphonyl Monochloro-1 : 4-3 : 6-*dianhydrodeoxysorbitol.*—The methanesulphonyl compound (0·12 g.), obtained by the lithium chloride reaction above, was heated with alcohol (5 c.c.) and 5% sodium hydroxide solution (15 c.c.) on the boiling water-bath for 1 hour. The solution was then neutralised with acetic acid and evaporated to dryness under reduced pressure and the residue extracted several times with boiling chloroform. The combined extracts were dried ($MgSO_4$) and on evaporation afforded a crystalline residue; recrystallisation of this from ether–light petroleum gave a monochlorodianhydrodeoxyhexitol in long needles, m. p. 63—65° alone or on admixture with the compound described by Overend, Montgomery, and Wiggins.

Action of Lithium Chloride on 2 : 5-*Ditoluene*-p-*sulphonyl* 1 : 4-3 : 6-*Dianhydrosorbitol.*—The ditoluene-*p*-sulphonyl compound (0·75 g.) was heated with anhydrous lithium chloride (0·3 g.), absolute alcohol (10 c.c.), and dry acetone (10 c.c.) at 150° for 48 hours. The solution was evaporated to dryness and the residue extracted with a mixture of chloroform and water. The chloroform extract was washed with water, dried ($MgSO_4$), and evaporated to a syrup (0·5 g.) which partly crystallised on being kept. Recrystallisation of the solid portion (0·12 g., 23%) from aqueous alcohol gave toluene-*p*-sulphonyl monochlorodianhydrodeoxysorbitol in stout needles, m. p. 94—95° alone or on admixture with the compound prepared by Overend, Montgomery, and Wiggins (*loc. cit.*).

Action of Lithium Chloride on 2 : 5-*Dimethanesulphonyl* 1 : 4-3 : 6-*Dianhydro*-L-*iditol.*—(i) The dimethanesulphonyl compound (0·5 g.) was heated with anhydrous lithium chloride (0·35 g.), absolute alcohol (10 c.c.), and dry acetone (10 c.c.) at 150° for 48 hours. The product, isolated in the same way as in the preceding experiments, was unchanged starting material (0·3 g., 60% recovery).

(ii) The dimethanesulphonyl compound (0·85 g.) was heated with anhydrous lithium chloride (0·55 g.), absolute alcohol (20 c.c.), and dry acetone (15 c.c.) in an autoclave at 180° for 48 hours. Treatment of the resulting solution in the usual way yielded only a black tar (0·16 g.) which showed no tendency to crystallise.

Treatment of 1 : 4-3 : 6-*Dianhydro*-L-*iditol with Thionyl Chloride.*—Dianhydro-L-iditol (2·25 g.) was dissolved in dry pyridine (5 c.c.), and thionyl chloride (2·2 c.c.) carefully added at 0°. The mixture was heated in an oil-bath to 95—100°, whereupon a vigorous reaction occurred; after the temperature had been kept at 100° for 2 hours, the mixture was cooled, poured into ice-water, and set aside overnight. The resulting suspension was extracted several times with chloroform, and the combined extracts were washed successively with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue obtained was negligible.

Action of Sodium on 2 : 4-3 : 5-*Dimethylene* 1 : 6-*Dichloro*-1 : 6-*dideoxysorbitol*.—The dichloro-compound (1 g.) (Haworth and Wiggins, *J.*, 1944, 58) was heated to its m. p., and clean sodium (0·2 g.) added in portions. The mixture was heated at 120° until it had become almost solid owing to the separation of sodium chloride, then diluted with dry toluene and refluxed for 2 hours. The toluene solution was decanted and the residue extracted several times further with boiling toluene. The combined extracts on evaporation yielded a syrup (0·8 g.) which crystallised on trituration with ether; recrystallisation from the same solvent gave the product as clusters of crystals, m. p. 96—97°, $[\alpha]_D^{15}$ +149·5° (*c*, 2·02 in chloroform). It decolorised alkaline potassium permanganate and a solution of bromine in chloroform. It was probably 2 : 4-3 : 5-*dimethylene* 1-*chloro*-1 : 6-*dideoxy*-5 : 6-*sorbitoleen* (Found: C, 46·5; H, 5·5; Cl, 17·0. $C_9H_{11}O_4Cl$ requires C, 46·5; H, 5·3; Cl, 17·2%). The syrupy residues were combined and re-treated with sodium (0·2 g.) as above. In this way a further quantity of crystalline material, m. p. 96—97°, was obtained. The total yield was 0·42 g. (50%).

Action of Sodium Iodide on 2 : 4-3 : 5-*Dimethylene* 1 : 6-*Dichloro*-1 : 6-*dideoxysorbitol*.—The dichloro-compound (0·5 g.) was dissolved together with dry sodium iodide (2 g.) in dry acetone (20 c.c.) and heated at 110° for 48 hours. Thereafter the solution was evaporated to dryness, the residue extracted with chloroform, and the extract washed successively with sodium thiosulphate solution and water. Evaporation of the solvent gave a solid residue which, recrystallised from alcohol, formed stout needles, m. p. 126—128°, $[\alpha]_D$ +19·2° (*c*, 2·28 in chloroform). The substance contained both chlorine and iodine and was probably 2 : 4-3 : 5-*dimethylene* 1-*chloro*-6-*iodo*-1 : 6-*dideoxysorbitol* (Found: C, 28·5; H, 3·5 $C_9H_{13}O_4ClI$ requires C, 28·7; H, 3·6%).

THE CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

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265. *The Kinetics of the Reduction of Aromatic Iodo-compounds by Hydriodic Acid in Solution.*

By V. GOLD and MARY WHITTAKER.

The replacement of the iodine atom by hydrogen through the action of hydriodic acid on some substituted *p*-iodophenols has been studied kinetically in acetic acid–water mixtures. The effect of methyl and chloro-groups on the reaction velocity is very similar to the known effect of these substituents on the velocity of nitration of aromatic compounds. It is concluded that the reduction is an electrophilic replacement of iodine.

THE iodine atom in an organic iodide may often be replaced by hydrogen by the use of hydriodic acid, $RI + HI \longrightarrow RH + I_2$. Some observations on the structural factors affecting the velocity of this reaction were made by Shoesmith and Slater (*J.*, 1924, **125**, 1312, 2278), who showed that the ease of reduction of the three isomeric iodophenols followed the sequence $p > o \gg m$, that iodoresorcinol was more reactive than any of the iodophenols, and that the series of iodo-hydrocarbons *o*-iodotoluene, *p*-iodotoluene, *m*-iodotoluene, iodobenzene was reduced with increasing difficulty in that order. A few facts have also been recorded on the related topics of the relative ease of reduction of some substituted benzyl bromides by means of hydriodic acid (Lapworth and Shoesmith, *J.*, 1912, **101**, 1391; Shoesmith and Slater, *loc. cit.*) and of the reduction of substituted aromatic halogeno-compounds by the use of hydrogen chloride alone and with stannous chloride (Nicolet *et al.*, *J. Amer. Chem. Soc.*, 1921, **43**, 2081: 1927, **49**, 1796, 1801, 1806, 1810). The reduction of some alkyl iodides by hydriodic acid in the gas phase has also been investigated kinetically (Ogg, *ibid.*, 1934, **56**, 526), but this probably constitutes a problem which has little in common with the solution reactions studied by us.

The present investigation deals with velocity measurements on the reduction of some further-substituted 4-iodophenols by means of hydriodic acid in aqueous acetic acid. The effects of changes in the structure of the aromatic iodide, and in solvent, temperature, and concentrations of the reactants were studied.

EXPERIMENTAL.

Materials.—*p*-Iodophenol was prepared from *p*-aminophenol (Dains and Eberley, *Org. Synth.*, Coll. Vol. II, 1943, p. 355) and purified by steam distillation and crystallisations from benzene. 4-*Iodo*-2-*methylphenol* (5-iodo-*o*-cresol) was synthesised from *o*-cresol by nitrosation (Bridge and Morgan, *J. Amer. Chem. Soc.*, 1898, **20**, 766), followed by reduction to 5-amino-*o*-cresol by use of ammoniacal hydrogen sulphide, and subsequent replacement of the amino-group by iodine by the Gattermann reaction as used for *p*-iodophenol. It was crystallised from carbon tetrachloride and finally from light petroleum (b. p. 60—80°); m. p. 64° (Found: C, 35·8; H, 3·0; I, 56·0. C_7H_7OI requires C, 35·9; H, 3·0; I, 54·3%).

4-Iodo-3-methylphenol (6-iodo-*m*-cresol) and 4-iodo-3-methyl-6-*iso*propylphenol (6-iodothymol) were prepared by analogous sequences of reactions starting from *m*-cresol and thymol (Kremers, Wakeman, and Hixon, *Org. Synth.*, Coll. Vol. II, p. 511), respectively: preparation by direct iodination of thymol (Datta and Prosad, *J. Amer. Chem. Soc.*, 1917, **39**, 444) was abandoned because of the unsatisfactory yield. Both substances were recrystallised from light petroleum.

2-Chloro-4-iodophenol was obtained by chlorination of *p*-iodophenol (Brazier and McCombie, *J.*, 1912, **101**, 968), followed by steam-distillation and crystallisation from carbon tetrachloride. It was also prepared from *o*-chlorophenol by the above sequence of nitrosation, reduction, and Gattermann replacement of the amino-group by iodine.

4-Iodo-2-nitrophenol, prepared from *p*-aminophenol by nitration of the acetyl derivative (Girard, *Bull. Soc. chim.*, 1924, **35**, 772), hydrolysis to 4-amino-2-nitrophenol, and introduction of iodine in place of the amino-group, was crystallised from light petroleum.

All the iodophenols prepared were free from iodine. Where necessary the last traces of iodine were removed by extraction of a solution in chloroform with dilute aqueous thiosulphate solution. Stock solutions in acetic acid were stable and produced no visible colour even on storage for several months.

Acetic acid was purified and made anhydrous by treatment with acetic anhydride as described by Orton and Bradfield (*J.*, 1927, 983) and fractionally distilled. Acetic anhydride was the AnalaR reagent.

Constant-boiling hydriodic acid (May and Baker) was freed from iodine by refluxing with red phosphorus and distillation in all-Pyrex apparatus immediately before use, the vapour being passed over a copper spiral. The constant-boiling fraction was collected and made into a stock solution in acetic

FIG. 1.

Illustration of procedure for evaluation of initial rates. (Expt. 109; see Table I.)

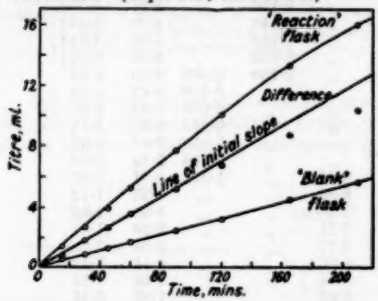
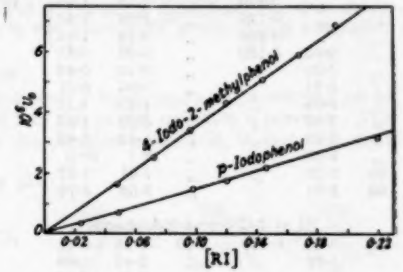


FIG. 2.

Dependence of initial rates upon concentration of aromatic iodide.



acid, with additions of acetic anhydride when it was desired to reduce the water content of the reaction mixture below the amount introduced with the constant-boiling hydriodic acid. The exact concentration of hydriodic acid was checked by a Volhard titration.

Kinetic Measurements.—The reactions were carried out in stoppered round-bottom flasks (150 ml.), coated black on the outside to exclude light and shaken mechanically in a thermostat bath. Each run was paralleled by a blank experiment with identical amounts and samples of solvents and hydriodic acid, but with the omission of the organic iodide. Both reactions were started by the final addition of a freshly prepared stock solution of hydriodic acid to the solutions in the reaction vessels. The progress of the reactions in both flasks was followed by periodically pipetting samples (7 ml.) into water (100 ml.), thus arresting the reaction, and titrating the liberated iodine with standard (~N/20) thiosulphate solution.

In most cases the amount of reaction in the blank vessel was appreciable, sometimes constituting more than half of the total reaction. This was allowed for in the following way. Let the velocity of the increase in iodine concentration in the reaction flask and in the blank flask be given by $(d[I_2]/dt)_{reaction} = -d[RI]/dt + k_B[HI]^n$ and $(d[I_2]/dt)_{blank} = k_B[HI]^n$, respectively. Since the concentration of hydriodic acid in the reaction flask will not be exactly the same as that in the blank flask at any time except at the start of the reaction, the velocity of reduction at any particular moment during the course of the reaction cannot be obtained by simple subtraction of these two equations. However, subtraction of these two sets of titres (corresponding to the same moment of time) from each other should lead to a rate of iodine formation which will approximate to the rate of disappearance of iodophenol the more closely the nearer are the points to the start of the reaction (provided that the iodophenol exerts no large effect on the "blank" oxidation of hydriodic acid). Initial rates (v_0) of iodophenol reduction were accordingly obtained from the relation

$$\begin{aligned} v_0 &= -(d[RI]/dt)_{t \to 0} \\ &= \{(d[I_2]/dt)_{reaction} - (d[I_2]/dt)_{blank}\}_{t \to 0} \\ &= \{d([I_2]_{reaction} - [I_2]_{blank})/dt\}_{t \to 0} \end{aligned}$$

The procedure is illustrated by a typical experiment in Table I and Fig. 1.

TABLE I.

Illustration of procedure for evaluation of initial rates.

(Expt. 109.) $[4\text{-Iodo-2-methylphenol}]_0 = 0{\cdot}096$M. $[H_2O] = 5{\cdot}94$M. $[HI]_0 = 1{\cdot}02$M. Temp. = 40°.

Titres refer to ml. of 0·0482N-$Na_2S_2O_3$ per 7-ml. sample.

Time, mins.	Titres. Reaction (R).	Blank (B).	$R - B$.	Time, mins.	Titres. Reaction (R).	Blank (B).	$R - B$.
15	1·41	0·60	0·81	90	7·72	2·49	5·23
30	2·73	0·88	1·85	120	10·04	3·25	6·79
45	3·97	1·30	2·67	165	13·34	4·58	8·76
60	5·30	1·70	3·60	210	16·01	5·67	10·34

Initial slope of graph in Fig. 1 = 0·0594 ml. $min.^{-1}$.

$$v_0 = 0{\cdot}0594 \times 0{\cdot}0482/(2 \times 7 \times 60) \text{ moles } l.^{-1} \text{ sec.}^{-1}$$
$$= 3{\cdot}41 \times 10^{-4} \text{ moles } l.^{-1} \text{ sec.}^{-1}.$$

TABLE II.

Initial rates (v_0) *and first-order rate constants* (k_1).

Temp.	$[H_2O]$.	$[RI]_0$.	$[HI]_0$.	10^4v_0.	10^3k_1.		Temp.	$[H_2O]$.	$[RI]_0$.	$[HI]_0$.	10^4v_0.	10^3k_1.	
RI = *p*-Iodophenol.							RI = 4-Iodo-2-methylphenol.						
40°	5·94	0·0240	1·02	0·35	1·48		40°	5·94	0·0480	1·02	1·67	3·48	
,,	,,	0·0490	,,	0·73	1·49		,,	,,	0·0720	,,	2·54	3·53	
,,	,,	0·0980	,,	1·52	1·55	Mean,	,,	,,	0·0960	,,	3·41	3·56	Mean,
,,	,,	0·120	,,	1·78	1·48	1·49	,,	,,	0·120	,,	4·31	3·59	3·55
,,	,,	0·146	,,	2·20	1·51		,,	,,	0·144	,,	5·09	3·53	
,,	,,	0·220	,,	3·16	1·44		,,	,,	0·168	,,	5·92	3·52	
,,	9·05	0·120	,,	0·37	0·31		,,	,,	0·192	,,	6·90	3·59	
,,	7·50	,,	,,	0·79	0·66		,,	,,	0·120	0·408	0·28	0·23	
,,	6·71		,,	1·05	0·87		,,	,,	,,	0·510	0·41	0·34	
,,	6·06	,,	,,	1·40	1·17		,,	,,	,,	0·612	0·81	0·67	
,,	5·63	,,	,,	2·20	1·83		,,	,,	,,	0·714	1·35	1·12	
,,	5·26	,,	,,	4·43	3·69		,,	,,	,,	0·816	2·00	0·67	
,,	4·49	,,	,,	12·7	10·6		,,	,,	,,	0·918	3·14	2·62	
30	5·26	,,	,,	1·41	1·17		,,	9·09	,,	1·02	0·81	1·67	
50	5·94	,,	,,	5·59	4·70		,,	8·26	,,	,,	1·35	1·12	
							,,	7·50	,,	,,	1·98	1·65	
RI = 2-Chloro-4-iodophenol.							,,	7·11	,,	,,	2·36	1·97	
40	5·94	0·120	1·02	~0·15	~0·12		,,	6·71	,,	,,	3·36	2·80	
,,	1·53	,,	,,	2·48	2·06		,,	6·06	,,	,,	4·11	3·42	
,,	0	,,	,,	8·91	7·42		,,	5·63	,,	,,	5·66	4·71	
30	0	,,	,,	3·94	3·28		,,	5·23	,,	,,	7·22	6·01	
50	0	,,	,,	19·6	16·3		30	5·94	,,	,,	1·47	1·23	
,,	$[Ac_2O]$ = 2·94	,,	,,	3·6	3·0		50	,,	,,	,,	14·2	11·8	
RI = 4-Iodo-3-methyl-6-*iso*propylphenol.							RI = 4-Iodo-3-methylphenol.						
20	5·94	0·120	1·02	~33	~28		20	5·94	0·120	1·02	9·03	7·5	
30	,,	,,	,,	~98	~82		30	,,	,,	,,	28·5	23·7	
,,	9·09	,,	,,	~86	~72		40	,,	,,	,,	85·1	71	

Results.—A summary of the experiments is given in Table II. The initial reaction velocity was found to be (*a*) proportional to the concentration of the iodophenol used; (*b*) approximately proportional to the cube of the stoicheiometric concentration of hydriodic acid used; (*c*) approximately inversely proportional to the 3·5th power of the molarity of water, at least at the high concentrations of water used; (*d*) unaffected by a large increase in surface area by packing the reaction vessel with glass-wool or by the presence of free iodine or the organic reaction product; and (*e*) decreased by the presence of free acetic anhydride in an anhydrous solvent. The proportionality (*a*) was verified for *p*-iodophenol ($[HI]_0 = 1{\cdot}02$M.; $[H_2O] = 5{\cdot}94$M.; 40°) and for 4-iodo-2-methylphenol under the same conditions (Fig. 2); (*b*) was found for 4-iodo-2-methylphenol ($[H_2O] = 5{\cdot}94$M.; $[RI]_0 = 0{\cdot}120$M.; 40°) (Fig. 3), and (*c*) for the same substance ($[HI]_0 = 1{\cdot}02$M.; $[RI]_0 = 0{\cdot}120$M.; 40°) (Fig. 4); (*d*) was verified for *p*-iodophenol and (*e*) for 2-chloro-4-iodophenol. These conclusions may be combined in the experimental rate equation

$$v_0 = k_0[RI][HI]_0^3/[H_2O]^{3\cdot5} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Experimental first-order rate coefficients, as listed in Table II, are defined as $k_1 = v_0/[RI]_0$, the units of v_0 being moles $l.^{-1}$ $sec.^{-1}$. The first-order dependence of the rate on the iodophenol concentration during the major portion of an experiment was also verified by evaluating first-order rate coefficients in the usual manner from the integrated form of the rate equation in an experiment in which $[HI]_0 \gg [RI]_0$ and for which the iodine liberation in the blank flask was very slow, so that [HI] could be taken as constant for the run.

The liberation of iodine by the action of hydriodic acid on 4-iodo-2-nitrophenol was found to be considerably more rapid than with any other compound used. However, the reaction occurring in this

case is the reduction of the nitro-group, and no information could be obtained about the speed of the iodine replacement, if it occurs at all.

FIG. 3.
Dependence of initial rate upon concentration of hydriodic acid.

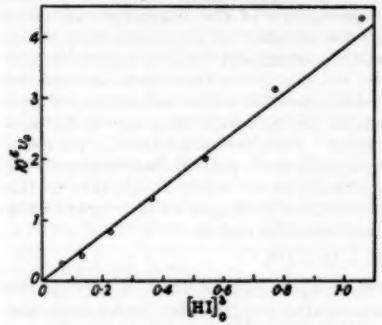
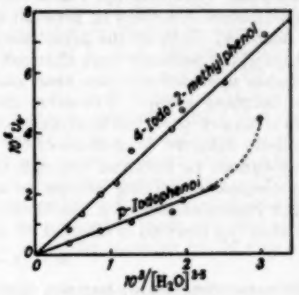


FIG. 4.
Dependence of initial rates upon concentration of water.

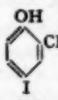
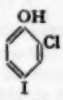
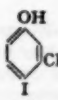
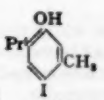


Treatment of iodobenzene and *p*-chloroiodobenzene (0·12M.) [in which the iodine atom is known to be replaceable by a nitro-group in preference to nitration at another position (Holleman, *Rec. Trav. chim.*, 1913, **34**, 222)] with anhydrous hydriodic acid (1·02M.) in acetic acid at 40° produced only a negligible amount of reduction after three days.

DISCUSSION.

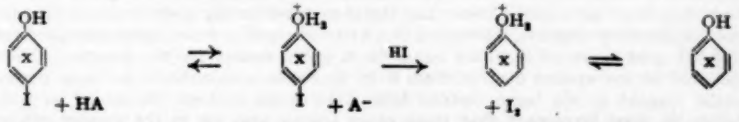
The structures studied (Table III) are all derived from *p*-iodophenol, and a comparison of the effect of different substituent groups introduced into this parent molecule is possible. The strong influence exerted by substituent groups on the reaction velocity is, in fact, the most

TABLE III.

Formula					
Relative rate of reduction	1	2·4	0·08	48	160

notable feature of the reaction. It is particularly significant that chlorine and methyl groups, introduced into the 2-position of *p*-iodophenol (where steric effects should be of minor importance), influence the reaction velocity in opposite senses, as they do, for example, in aromatic nitration. The reaction is, therefore, clearly not homolytic in character.

We may next ask whether the increase in reactivity on introducing an electron-repelling group (and the converse effect) can be due to an increased (decreased) basicity of the phenolic hydroxyl group, the compound reacting in the strongly acid media considered *via* the formation of its conjugate acid in a low concentration, *i.e.*:



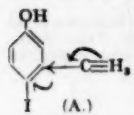
Although such a mechanism would help to explain the high reaction order with respect to hydriodic acid, it seems to be ruled out by Shoesmith and Slater's observation that the velocity of reduction is increased by introducing a methyl group also into iodobenzene, and in this case the methyl group cannot act by strengthening a basic grouping. The polar effect of the substituents must therefore be concerned with the actual substitution stage.

As has been pointed out by Hughes and Ingold on a number of occasions (*e.g.*, Hughes, Ingold, and Shapiro, *J.*, 1936, 225), the electronic requirements of a bimolecular heterolytic reaction cannot *a priori* be predicted with certainty, since attachment of the new group and detachment of the replaced group are helped by the movement of electrons in opposite directions.

Thus a substitution reaction which is accelerated by the introduction of electron-repelling methyl groups and retarded by the introduction of chlorine into the nucleus, like the reductions considered in this paper, may be brought about either by electrophilic attack, if the electronic effect on the proton attachment phase is more important, or by nucleophilic attack if the electronic effect on the iodide detachment phase is the bigger effect. It is found that, for substitution reactions in general, the electronic requirements of the attachment are more often decisive; those of the detachment only dominate the situation for reactions which, if the structure of the molecule were changed but slightly, would proceed according to a unimolecular mechanism in which the rate-determining stage of the reaction is the heterolytic detachment of the outgoing group. However, the nucleophilic replacement of iodine in substituted aryl iodides is known (*e.g.*, the hydrolysis of *p*-iodonitrobenzene by hydroxide ions) and its features are entirely different from those of the reduction reactions. Thus the iodine atom in the iodophenols cannot be removed through the agency of hydroxide ions, nor can iodobenzene with strong electron-attracting groups be reduced with hydriodic acid. This, in addition to the inherent improbability of a mechanism which would introduce hydrogen as H^-, leaves little doubt that the reaction is effected by electrophilic attack upon the carbon atom: *

$$R-\overset{\cdot\cdot}{I}+H\overset{\cdot\cdot}{-}X\longrightarrow R-H+I^+X^-$$

The same conclusion, namely, that the substituent group exerts its effect mainly on the approach phase of the reaction, is also supported by a comparison of the rates for 4-iodo-2- and -3-methylphenol. The effect of the methyl group is seen to be much greater when it is *ortho* to the iodine atom than when it is in the *meta*-position, the operation of the electron release increasing the electron availability at the carbon atom next to the iodine atom (see A). It is remarkable that 4-iodo-3-methylphenol is the more easily reduced compound in spite of the fact that methyl substitution in the *ortho*-position relative to the substitution centre of the reaction may introduce some steric hindrance. This interpretation also explains the sequence found by Shoesmith and Slater for the reduction of the isomeric iodotoluenes and iodophenols.



(A.)

The possible reaction mechanism

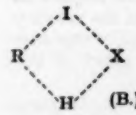
$$R\overset{\cdot\cdot}{-}I+X\longrightarrow R^+ + IX^-$$

in which the rate-determining stage is a bimolecular electrophilic replacement on iodine would not be expected to lead to RH as final product, since H^- is not easily abstracted from the reaction medium and other bases are present in the solvent (phenyl acetate could be a product, for example). The same objection would not apply to the alternative scheme

$$R-\overset{\cdot\cdot}{I}+X\longrightarrow R^- + IX^+$$

and certain features of it are used in the following paragraph. It is unlikely to be a good description of the reaction by itself, since it again leads to difficulties concerning the effect of substituent groups on the velocity. Also, the reducing power of the reagent X should then follow its general nucleophilic activity, which is not observed.

Although the electrophilic attack on the aromatic molecule appears to account for the most structure-sensitive contribution to the activation energy of the reaction, the same or another reagent molecule appears to be involved in the transition state (as a nucleophilic reagent) for the removal of the ejected I^+. If this were not so, the efficiency of the reagent should merely depend on its potency as a proton donor and therefore other strong acids besides hydriodic acid should be deiodinating reagents, whereas in fact hydriodic acid is an exceptionally good reagent and sulphuric acid in acetic acid, for example, is quite useless for the purpose. However, hydriodic acid or any species derived from it in the medium is unlikely to be as powerful a nucleophilic reagent as the bases derived from the solvent system. A reason why it may nevertheless be more important that these other species may lie in the greater entropy of activation for its reaction, such as would arise if electrophilic and nucleophilic reactivity were combined in a single reagent molecule to give a transition state as shown in (B). Intervention of another molecule for the purpose of removing I^+ would involve either a reaction with two successive bimolecular stages or a termolecular process, and both these alternatives would have a lower *a priori* probability. For a highly organised transition state like (B), geometrical factors, such as the relative bond lengths of R–I and H–X may be very critical and



(B.)

* On our picture the phenoxide ion should be most readily reduced but its concentration in our acidic reaction medium must be quite insignificant.

thus lead to maximum reactivity in a molecule which would not have been regarded as the most efficient reagent on purely electrostatic considerations.

The identity of the reagent HX which is believed to effect the reduction in a single-stage process is not certain. It seems improbable that the curious kinetic relationship (1) is related to the mechanism of the reaction in a straightforward way; it is more likely to be a complex consequence of employing a solvent system of several components. In dry acetic acid hydrogen iodide may, in the main, be in the form of HI molecules, but the addition of an excess of water probably results in a high degree of conversion into H_3O^+ and I^- ions, leaving only a small amount of HI molecules. For various reasons the species I^-, I_3^-, H_3O^+, $AcOH_2^+$, HI_2^- can all be ruled out as feasible reagents, so that the effect of water must be to reduce the concentration of the effective reagent which is either hydrogen iodide or a species derived from it by a reaction other than the loss of a proton (cf. the experimentally observed strong retardation of the reaction by the addition of water). The chemical species which appear to be the most likely reagents are HI and H_2I^+, but we cannot decide between them on our experimental evidence. Both these reagent molecules would fit into kinetic schemes involving the concentration of hydriodic acid to a power higher than unity. The scheme involving H_2I^+, in particular, leads to a rate equation which is very similar to the experimental one (1), but it would be unjustifiable to rule out HI on this ground alone.

The high reaction order *may* arise in the following way. In the presence of water the equilibrium $HI + H_2O \rightleftharpoons H_3O^+ + I^-$ (equilibrium constant, K_1) probably lies largely over on the right-hand side, and since, under the conditions for which the high reaction order with respect to the stoicheiometric concentration of hydrogen iodide ($[HI]_{st}$) was found,

$$[H_2O] \gg [HI]_{st}$$
$$[H_3O^+] \sim [I^-] \sim [HI]_{st} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

if we make the assumption that the reaction $H_2O + AcOH \longrightarrow H_3O^+ + OAc^-$ is relatively unimportant. This may be regarded as a fair first approximation in view of the poor conductivity of slightly wet acetic acid. Therefore,

$$[HI] = \frac{1}{K_1} \cdot \frac{[HI]_{st}^2}{[H_2O]} \cdot \frac{f_\pm^2}{f_{H_2O} \cdot f_{HI}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

and

$$v = k[RI][HI] = \frac{k}{K_1}[RI] \frac{[HI]_{st}^2}{[H_2O]} \cdot \frac{f_\pm^2}{f_{H_2O} \cdot f_{HI}}$$

For a reaction involving the hypothetical species H_2I^+ we must also consider the equilibrium $2HI \rightleftharpoons H_2I^+ + I^-$ (equilibrium constant, K_2), which certainly would lie largely on the left-hand side, and hence obtain for the velocity of the reaction

$$v = k[H_2I^+][RI] = \frac{kK_2}{K_1^2} \frac{[RI][HI]_{st}^2}{[H_2O]^2} \cdot \frac{f_{H_2O^+}}{f_{H_2I^+}} \cdot \frac{f_{H_2O^+} \cdot f_{I^-}}{f^2_{H_2O}} \quad . \quad . \quad . \quad . \quad . \quad (4)$$

which, apart from the solvent effect on the reaction velocity, is a good description of the experimental kinetic relationship (1). Although we believe the explanation of the high reaction order to lie somewhere along these or similar lines, we cannot claim, on the present data and the approximate treatment given, to have established a proof for either HI or H_2I^+ molecules as reagents. Having regard to the structure of the probable transition state (B), the HI molecule itself would appear to be the more plausible reagent species. Also, it must be admitted that there seems to be little evidence for the existence of H_2I^+ from any other field.

The activation energies for different substances (Table IV) follow the reverse sequence of the rates but the series is not quite isentropic. The activation energy for *p*-iodophenol is seen to increase with the water content of the medium. The low activation energy for 2-chloro-4-iodophenol need therefore not be anomalous, since it alone refers to an anhydrous solvent. The values given have therefore only comparative significance.

TABLE IV.

Activation energies.

Substance.	$[H_2O]$, M.	*E*.	Temp. range.	Substance.	$[H_2O]$, M.	*E*.	Temp. range.
p-Iodophenol	5·94	22·8	40—50°	4-Iodo-3-methylphenol	5·94	20·7	20—40°
	5·26	22·0	30—40	6-Iodothymol	5·94	19	20—30
4-Iodo-2-methylphenol	5·94	22·2	30—50	2-Chloro-4-iodophenol	0	15·7	30—50

It is noteworthy that the electronic requirements for iodine replacement and the replacement of a hydrogen atom by a nitro-group are also quantitatively very similar, as is seen if the effects

of a substituent group on deiodination and nitration *at a given position* relative to a substituent group are compared, *e.g.*, by considering the following partial rate factors in the case of nitration.

Comparison of influence of substituent groups on rates of deiodination reduction and aromatic nitration.

Group X and its position relative to replaced I and H.	Reduction (replacement of I).	Nitration (replacement of H).
H (standard)	1	1
m-Methyl	2·4	3·0 [1]
o-Methyl	48	40 [1]
m-Chloro	0·08 *	0 [2]

[1] Ingold, Lapworth, Rothstein, and Ward, *J.*, 1931, 1959.
[2] Bird and Ingold, *J.*, 1938, 918.
* This value is the least accurate result for reduction velocities owing to the importance of the "blank" correction in experiments using the same solvent as for the other iodophenols. The other measurements on 2-chloro-4-iodophenol reported in this paper relate to a dry solvent in which a study of the more reactive iodophenols is impossible.

KING'S COLLEGE, LONDON, W.C.2. [*Received, December 7th*, 1950.]

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266. *Studies in the Sterol Group. Part LI.* Reactions between 17-Keto-steroids and Organometallic Compounds.*

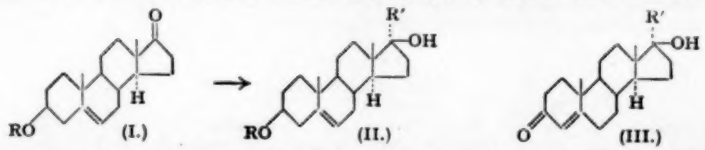
By C. W. GREENHALGH, H. B. HENBEST, and E. R. H. JONES.

The reaction between 17-keto-steroids and Grignard reagents (other than methyl) is known to lead chiefly to reduction of the carbonyl group. It has now been found that the reaction between dehydro*epi*androsterone (the 3β-hydroxyl-group being protected as a tetrahydropyranyl ether) and various alkyl-lithium compounds leads to less reduction, and that 17α-alkyl-17β-alcohols can thus be prepared in moderate yields.

Dehydro*epi*androsterone undergoes a Reformatsky type of reaction with propargyl bromide, to give the 17α-propargyl-17β-alcohol. Hydrolysis and Oppenauer oxidation yield 17α-propargyltestosterone, a homologue of the progesterone substitute, 17α-ethynyltestosterone.

IT is now well established that the reaction between 17-keto-steroids and nucleophilic reagents leads predominantly to 17α-substituted 17β-hydroxy-compounds (cf. Shoppee, *Ann. Reports*, 1946, **43**, 200), the reaction being envisaged as taking place by "rear attack" at $C_{(17)}$. For example, the reaction of dehydro*epi*androsterone (I; R = H) with potassium acetylide in liquid ammonia gives a 50% yield of the 17α-ethynyl compound (Ruzicka and Hofmann, *Helv. Chim. Acta*, 1937, **20**, 1280), accompanied by less than 1% of the 17β-isomer (Meystre and Reichstein, *ibid.*, 1939, **22**, 728). Similarly, ethoxyacetylene gives the 17α-ethoxyethynyl compound in good yield (65%) (Heusser, Eichenberger, and Plattner, *ibid.*, 1950, **33**, 370).

The reaction between 17-keto-steroids and Grignard reagents has been investigated by Butenandt and by Ruzicka and their collaborators. 17α-Methyl-17β-alcohols are obtained in satisfactory yields (65%) (Ruzicka, Goldberg, and Meyer, *ibid.*, 1935, **18**, 994), but with ethylmagnesium halides the expected 17α-ethyl-17β-alcohol is accompanied by the product formed by reduction of the 17-keto-group (mainly 17β-hydroxy-compound) (Butenandt, Schmidt-



Thomé, and Paul, *Ber.*, 1938, **71**, 1313; 1939, **72**, 1112). With *n*-propylmagnesium iodide, reduction of the 17-keto-group is the main reaction, the 17α-*n*-propyl compound not being isolated (Ruzicka and Rosenberg, *Helv. Chim. Acta*, 1936, **19**, 357). Allylmagnesium bromide

* Part L, *J.*, 1948, 1798.

gives a very good yield (90%) of the 17α-allyl derivative (Butenandt and Peters, *Ber.*, 1938, **71**, 2688).

Organolithium reagents will often undergo normal 1 : 2-addition to many hindered ketones that are reduced by Grignard reagents (cf. Wittig and Thurtle, " Newer Methods of Preparative Organic Chemistry," Interscience Publ. Inc., New York). The reaction between dehydro-*epi*androsterone (I; R = H) and certain alkyl-lithium compounds has therefore been investigated in the expectation that an improved route to 17-alkyl-carbinols would result. A general method for elaborating 17-alkyl side-chains could then be envisaged, for dehydration of the 17-alkyl-carbinols to $\Delta^{17(20)}$-compounds (cf. Butenandt, Schmidt-Thomé, and Paul, *loc. cit.*), followed by hydrogenation (a further example of " rear attack "; cf. Plattner, Bucher, and Hardegger, *Helv. Chim. Acta*, 1944, **27**, 1177) would lead to 17-alkyl substituents possessing the natural β-configuration.

Accordingly, the reaction between *n*-propyl-lithium and dehydro*epi*androsterone was investigated in various solvents. In each case, an insoluble, unreactive complex resulting from the reaction of the organolithium compound with the 3-hydroxyl group was quickly precipitated. Fairly prolonged reaction gave a 5% yield of the 17α-*n*-propyl compound (II; R = H, R′ = Pr^n) in ethereal solution and an 8% yield in benzene solution, most of the ketone being recovered unchanged. Fieser and Huang-Minlon (*J. Amer. Chem. Soc.*, 1949, **71**, 1840) have recently mentioned that the reaction between dehydro*epi*androsterone and ethyl-lithium gives a low yield of the 17α-ethyl compound, but no experimental details were recorded.

To avoid the formation of insoluble complexes, the 3β-hydroxyl group was protected by formation of an adduct with 2 : 3-dihydropyran (Woods and Kramer, *ibid.*, 1947, **69**, 2246), such adducts being stable to organometallic reagents (Parham and Anderson, *ibid.*, 1948, **70**, 4187). Dehydro*epi*androsterone and cholesterol both formed adducts in high yields, from which the parent alcohol could be quantitatively recovered by treatment with methanol containing a little hydrochloric acid. Owing to the formation of a new centre of asymmetry in the pyran ring, each of these adducts might be expected to be a mixture of two stereoisomeric forms. The total dehydro*epi*androsterone adduct (m. p. 160—165°) was resolved by fractional crystallisation into about equal amounts of the two stereoisomers (m. p.s 188° and 176°; on admixture the melting point fell to 164—168°). The rotations of the two isomers were very noticeably different (−53° and +47°). The crystalline cholesterol adduct also appeared to be a mixture (from its melting point behaviour), but it was not easily resolvable by crystallisation.

The dihydropyran adduct of dehydro*epi*androsterone with various alkyl-lithium compounds (primary straight-chain alkyl groups only were used, R′ = Et, Pr^n, and n-C_8H_{17}) in homogeneous solution readily gave pure 17α-alkyl compounds in about 20% yield, independent of the nature of the alkyl group, reaction conditions, or method of isolation. The *n*-octyl compound is of interest for it should be possible to convert it into an isomer of cholesterol containing an unbranched side chain.

In these reactions with alkyl-lithium derivatives, reduction of the 17-keto-group was apparently the main side-reaction. Although no pure compounds were isolated after separation of the 17-alkyl compounds, the presence of 3β : 17-dihydroxyandrost-5-ene(s) in the mixture was indicated by means of a characteristic colour test devised by Boscott (*Nature*, 1948, **162**, 577). This colour test was found to be a satisfactory way of differentiating between secondary and tertiary $C_{(17)}$alcohols, and was also of use in assessing roughly the proportion of each in a mixture.

Reformatsky reactions can also be carried out with 17-keto-steroids, ethyl bromoacetate giving a 50% yield of hydroxy-ester (Reichstein, Müller, Meystre, and Sutter, *Helv. Chim. Acta*, 1939, **22**, 741). Propargyl bromide has recently been shown to undergo a Reformatsky type of reaction with various carbonyl compounds (Zeile and Meyer, *Ber.*, 1942, **75**, 356; Henbest, Jones, and Walls, *J.*, 1949, 2696; 1950, 3646). It was of interest to carry out this reaction with dehydro*epi*androsterone acetate (I; R = Ac) because Oppenauer oxidation of the 17-propargyl-3 : 17-diol obtained on hydrolysis should give a homologue of the orally active progestational compound 17α-ethynyltestosterone (pregneninolone). The reaction between dehydro*epi*androsterone acetate and propargyl bromide has been found to proceed readily in dioxan in the presence of zinc dust, to give a 40—50% yield of the 17α-propargyl compound (II; R = Ac; R′ = $CH_2{\cdot}C{\equiv}CH$). Hydrolysis then gave the corresponding 3β : 17β-diol, which was converted by Oppenauer oxidation into 17α-propargyltestosterone (III; R′ = $CH_2{\cdot}C{\equiv}CH$). The configuration of these compounds was shown to be the same as that of the 17α-alkyl compounds prepared by the Grignard or alkyl-lithium methods, by

mild hydrogenation of the propargyl-diol, the 17α-*n*-propyl compound (II; R = H, R′ = Pr^n) being produced in high yield. This compound was also prepared by hydrogenation of the allyl analogue (II; R = H, R′ = $CH_2{\cdot}CH{=}CH_2$) under the same conditions.

Experimental.

(All rotations were measured in chloroform solutions unless otherwise stated. M. p.s were determined on a Kofler block and are corrected.)

3β-2′-Tetrahydropyranyloxycholest-5-ene.—2 : 3-Dihydropyran (20 c.c.; purified by agitation with potassium hydroxide pellets, followed by distillation) was added to a solution of cholesterol (50 g.) in chloroform (150 c.c.), followed by phosphorus oxychloride (0·3 c.c.). The solution was warmed to 30°; a mildly exothermic reaction took place, the temperature rising to 38°. The solution was kept until the temperature had fallen to 30°, whereafter it was shaken with sodium carbonate solution to remove acidic materials. The solvent was evaporated *in vacuo*, and the solid residue recrystallised from ethyl acetate, to give *3β-2′-tetrahydropyranyloxycholest-5-ene* (48 g.) as needles, m. p. 155—160°, $[\alpha]_D^{14}$ −27° (*c*, 1·64) (Found: C, 81·5; H, 11·5. $C_{32}H_{54}O_2$ requires C, 81·65; H, 11·55%).

Hydrolysis of this adduct was effected by adding a solution of concentrated hydrochloric acid (0·25 c.c.) in ethanol (10 c.c.) to a suspension of the compound (0·2 g.) in ethanol (5 c.c.). Warming to 50° gave a clear solution from which cholesterol (m. p. and mixed m. p. 145—147°) was obtained by cooling and addition of a little water.

3β-2′-Tetrahydropyranyloxyandrost-5-en-17-one.—Concentrated hydrochloric acid (3 drops) was added to a solution of dehydro*epi*androsterone (3·6 g.) in purified 2 : 3-dihydropyran (25 c.c.). The mixture was kept at room temperature for 1½ hours and then made alkaline with methanolic potassium hydroxide, and the product precipitated by the addition of aqueous methanol. A single recrystallisation from methanol gave the adduct (3·0 g.) as needles, m. p. 169—170°. This product is a mixture of two stereoisomers; repeated recrystallisation from methanol resulted in the isolation of the higher-melting *isomer* as flat needles, m. p. 187—188·5°, $[\alpha]_D^{22}$ −53° (*c*, 4·92) (Found: C, 77·35; H, 10·0. $C_{24}H_{36}O_3$ requires C, 77·4; H, 9·75%).

One pure stereoisomer having been isolated it was possible to obtain the other in a state of purity. Concentrated hydrochloric acid (one drop) was added to a solution of dehydro*epi*androsterone (1 g.) in 2 : 3-dihydropyran (4 c.c.). After 1 hour at room temperature, the solution was seeded with the isomer, m. p. 187—188·5°, which induced rapid crystallisation. The mixture was then made alkaline with methanolic potassium hydroxide (2 c.c.), and the crystalline product (0·5 g.), m. p. 183—189°, collected and washed with cold nitromethane. Two recrystallisations from nitromethane brought the m. p. to 187—188·5°. The mother-liquor from the reaction mixture was concentrated to give a solid product (0·43 g.), m. p. 171—175°, which after three recrystallisations from nitromethane gave the lower-melting *isomer* as flat needles, m. p. 175—176°, $[\alpha]_D^{22}$ + 47° (*c*, 2·16) (Found: C, 77·6; H, 9·85%). A mixture of the epimers melted at 164—168°.

3β : 17β-Dihydroxy-17α-ethylandrost-5-ene (II; R = H, R′ = Et).—In this and succeeding experiments solutions of alkyl-lithium compounds were prepared in light petroleum (b. p. 80—95°) by Fieser and Gates's procedure (*J. Amer. Chem. Soc.*, 1940, **62**, 2335), the lithium being beaten into thin sheets. After determination of the strength of the solution by addition to water followed by titration with acid, a suitable volume of the solution was used in the experiment. 3β-2′-Tetrahydropyranyloxyandrost-5-en-17-one (1·0 g.; m. p. 169—170°) was dissolved in light petroleum (50 c.c.; b. p. 80—95°), and a solution of ethyl-lithium (0·19 g., 10% excess) in light petroleum (25 c.c.) was added rapidly. A voluminous white precipitate formed which dissolved on the addition of dry ether (25 c.c.). The pale yellow solution was kept at room temperature in a stoppered flask for 48 hours; a test sample then gave a negative Zimmerman test. The above operations were performed in an atmosphere of nitrogen. The steroid was isolated with ether, and the gummy solid obtained was dissolved in methanol (5 c.c.). Concentrated hydrochloric acid (2 drops) was added and the solution was warmed at 50° for 3 minutes. Addition of water gave a solid product (0·86 g.) which was chromatographed on alumina (120 g., P. Spence, type O; solvent, 1 : 1 ether–benzene). Ether–benzene (1 : 1) eluted an inappreciable amount of material, but ether eluted a solid (280 mg.; m. p. 189—193°). Two recrystallisations of this product from ethyl acetate–methanol gave the 17α-ethyl-3β : 17β-diol as needles, m. p. 198—199°, $[\alpha]_D^{21}$ −66° (*c*, 3·22 in ethanol). Butenandt, Cobler, and Schmidt (*Ber.*, 1936, **69**, 448) give m. p. 198°; Ruzicka, Hofmann, and Meldahl (*Helv. Chim. Acta*, 1938, **21**, 597) give m. p. 200—202°, $[\alpha]_D$ −68·4° (*c*, 1·16 in ethanol) for a sample prepared by hydrogenation of the 17α-ethynyl compound.

Acetylation of the ethyl-diol gave the 3β-acetate as plates (from methanol), m. p. 164—165·5°, $[\alpha]_D^{19}$ −85° (*c*, 0·4). Butenandt, Schmidt-Thomé, and Paul (*loc. cit.*) give m. p. 167—168°.

Further elution of the chromatogram in the above experiment with ether–methanol gave a gummy solid which in the Boscott colour test gave a magenta colour with no appreciable green fluorescence, indicating the presence of one or both of the 3β : 17-dihydroxyandrost-5-enes, and the absence of the 17α-ethyl-diol.

3β : 17β-Dihydroxy-17α-n-propylandrost-5-ene (II; R = H, R′ = Pr^n).—A solution of *n*-propyl-lithium (0·5 g.) in light petroleum (15 c.c.; b. p. 80—95°) was added rapidly to a stirred solution of 3β-2′-tetrahydropyranyloxyandrost-5-en-17-one (180 mg.; m. p. 187—188·5°) in light petroleum (15 c.c.; b. p. 80—95°) in an atmosphere of nitrogen. The slightly opalescent mixture was stirred at 80° for 4·5 hours during which the reaction mixture became yellow and a small amount of white solid was precipitated. The steroid was isolated with ether to give a solid, which after removal of the protecting group by treatment with methanolic hydrochloric acid gave a product which on recrystallisation from nitromethane gave the propyl-diol (102 mg.), m. p. 181—183°. Further recrystallisation from nitromethane–methanol gave the pure *diol*, m. p. 190—191·5°, $[\alpha]_D^{18}$ −76° (*c*, 0·60) (Found: C, 79·35; H, 10·8. $C_{22}H_{44}O_2$ requires C, 79·45; H, 10·9%).

In one experiment the intermediate dihydropyran adduct was isolated, and recrystallised from nitromethane–methanol to give plates, m. p. 157—159°.

The mother-liquor from the first recrystallisation gave a strong positive test for 3β : 17-dihydroxyandrost-5-ene in the Boscott colour test.

3β : 17β-*Dihydroxy*-17α-n-*octylandrost-5-ene* (II; R = H, R′ = *n*-C_8H_{17}).—3β-2′-Tetrahydropyranyloxyandrost-5-en-17-one (120 mg.; m. p. 164—168° or 186—188°) was dissolved in light petroleum (5 c.c.; b.p. 80—95°) by gentle warming, and the solution cooled to room temperature, some of the adduct crystallising. A solution of *n*-octyl-lithium (0·24 g.) in light petroleum (10 c.c.; b. p. 80—95°) was added rapidly—a white precipitate first formed which soon redissolved. The clear solution was kept at room temperature in a stoppered flask for 48 hours. Decomposition with water and isolation with ether gave a solid product. Hydrolysis of the protecting group by the method described previously gave a product which on trituration with nitromethane–methanol gave a gum. This was purified by placing it on a porous tile above light petroleum (b. p. 60—80°) in a closed container. The solid (40 mg.), m. p. 128—135°, was recrystallised from nitromethane–methanol, to give the pure *diol* as needles, m. p. 145—146°, $[\alpha]_D^{20}$ −55° (*c*, 0·40) (Found : C, 79·5, 80·9; H, 11·4, 10·7. $C_{27}H_{46}O_2$ requires C, 80·5; H, 11·5%). The yield could probably be improved by chromatography of the reaction product.

3β-*Acetoxy*-17β-*hydroxy*-17α-*propargylandrost-5-ene* (II; R = Ac, R′ = $CH_2{\cdot}C{\equiv}CH$).—Zinc dust (3 g.) was activated by stirring it with 2N-hydrochloric acid until effervescence commenced, the metal then being washed in turn with water, methanol, and dry ether. Dry dioxan (30 c.c.) and dehydro*epi*androsterone acetate (1·47 g.) were added immediately to the zinc, and some of the solvent (15 c.c) was removed by distillation to remove traces of moisture. Freshly distilled propargyl bromide (4·1 c.c.) was added dropwise to the boiling mixture. The reaction proceeded exothermally and the mixture became dark and viscous. When the reaction had subsided, the mixture was cooled and benzene and 2N-hydrochloric acid were added. The aqueous layer was again extracted with benzene, and the benzene extracts were evaporated *in vacuo* to give a dark tar. This tar was extracted with four 50-c.c. portions of hot light petroleum (b. p. 80—100°), and the filtered extracts were evaporated *in vacuo*, leaving a residue which solidified on trituration with methanol. Crystallisation from ethanol (together with chromatographic purification if the product was still rather dark) gave 3β-*acetoxy*-17β-*hydroxy*-17α-*propargylandrost-5-ene* as needles (0·57 g.), m. p. 147—148°, $[\alpha]_D^{20}$ −81° (*c*, 3·53) (Found : C, 77·15; H, 9·2. $C_{24}H_{34}O_3$ requires C, 77·8; H, 9·25%). Low analytical values for carbon are often obtained with propargyl-carbinols (Henbest, Jones, and Walls, *loc. cit.*).

Concentration of the mother-liquors gave a further 0·2 g. of the same quality. The yield based on keto-steroid was thus 45%. The propargyl compound gave a precipitate with ammoniacal silver nitrate in methanol, confirming the presence of an ethynyl group.

The rate at which the Reformatsky reaction proceeded was considerably influenced by the state of sub-division of the zinc dust, finer particle size leading to a faster and smoother reaction. Zinc wool gave no appreciable reaction.

3β : 17β-*Dihydroxy*-17α-*propargylandrost-5-ene* (II; R = H, R′ = $CH_2{\cdot}C{\equiv}CH$).—The above acetate (0·4 g.) was refluxed in methanol (11 c.c.) containing potassium hydroxide (0·28 g.) for 30 minutes. Water was added to the reaction mixture to precipitate the product (0·38 g.), m. p. 152—154°. Recrystallisation from ethanol or nitromethane gave the *diol* as flat needles, m. p. 156—157°, $[\alpha]_D^{18}$ −81° (*c*, 2·31) (Found : C, 79·85; H, 9·8. $C_{22}H_{32}O_2$ requires C, 80·5; H, 9·8%).

17β-*Hydroxy*-17α-*propargylandrost-4-en*-3-*one* (III; R′ = $CH_2{\cdot}C{\equiv}CH$).—The foregoing diol (0·29 g.) was dissolved in pure dry acetone (12 c.c.) and a solution of aluminium *tert.*-butoxide (1·1 g.) in dry benzene (22 c.c.) was added, the mixture then being heated under reflux for 5½ hours. The product was isolated with ether in the usual manner and chromatographed on alumina (90 g.; P. Spence, type O; solvent, benzene). Development with ether gave the crude ketone, which after two recrystallisations from methanol gave 17β-*hydroxy*-17α-*propargylandrost-4-en*-3-*one* (0·18 g., 60%) as needles, m. p. 135—137°, $[\alpha]_D^{20}$ +63° (*c*, 1·66) (Found : C, 80·4; H, 9·5. $C_{22}H_{30}O_2$ requires C, 80·95; H, 9·25%). Light absorption in EtOH : Maximum, 2400 A.; ε = 15,800.

As expected, the molecular-rotation differences between the above compounds are normal, *i.e.*, the 17α-propargyl-17β-hydroxy-groups do not exert a detectable vicinal effect at the 3-position : $[M_D]$3β-acetate (−300°) − $[M_D]$3β-sterol (−266°) = − 34° [Barton's (*J.*, 1945, 813) value, −35°]. $[M_D]\Delta^4$-3-ketone (+205°) − $[M_D]$3β-sterol (−266°) = +471° (Barton's value, +480°).

Partial Hydrogenation of 3β : 17β-*Dihydroxy*-17α-*propargylandrost-5-ene*.—The diol (17 mg.), dissolved in ethanol (5 c.c.), was hydrogenated in a micro-apparatus with a platinic oxide catalyst at room temperature and pressure. The uptake after 18 hours was 2·44 c.c. (corrected to N.T.P.) (theor. for two double bonds, 2·37 c.c.). The catalyst was removed by filtration, and the filtrate evaporated *in vacuo*, to give 3β : 17β-dihydroxy-17α-*n*-propylandrost-5-ene as needles, m. p. 190—191°, $[\alpha]_D^{18}$ −76° (*c*, 0·60). The m. p. was not depressed on admixture with an authentic sample prepared from dehydro*epi*androsterone and *n*-propyl-lithium (see above).

By using the same apparatus and experimental conditions, 17α-allyl-3β : 17β-dihydroxyandrost-5-ene [prepared from dehydro*epi*androsterone and allylmagnesium bromide by the procedure of Butenandt and Peters (*loc. cit.*)] took up one molecule of hydrogen, to give the same 17α-*n*-propyl compound, m. p. and mixed m. p. 189—190°.

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267. *Thermal Interchange of Acyl Groups in Triglycerides.*

By C. Barker, R. V. Crawford, and T. P. Hilditch.

β-Oleodistearin, when heated in an inert atmosphere at about 300°, is converted in about ten hours into a mixture of tristearin, oleodistearins, stearodioleins and triolein in proportions which are close to those deduced from probability considerations for a "randomly" distributed mixture of stearo- and oleo-glycerides. Acyl interchange is thus effected thermally and without catalyst at 300° in the same manner as it proceeds at lower temperatures in presence of catalysts such as sodium alkoxides or stannous and some other hydroxides. The thermally stimulated interchange of acyl groups is accompanied by a small but steady liberation of free fatty acids at the rate of about 1% per hour.

It has been recognised for many years that the acyl groups of a mixture of triglycerides may migrate, and a new mixture of mixed triglycerides be produced, at temperatures usually ranging from about 200° to 250° in presence of small proportions of a suitable catalyst (alkali alkoxides or hydroxide, certain compounds of tin, cadmium, or zinc, etc.). The same change proceeds, although relatively slowly, at 180° in presence of catalytic nickel during hydrogenation (Atherton and Hilditch, *J.*, 1941, 527). It is of some importance in connection with the thermal polymerisation ("heat-bodying") of drying oils to know whether at the temperatures (290—300°) employed in this process acyl migration or interchange of this kind may take place amongst the glyceride molecules without the intervention of a specific catalyst. It has often been indicated (*e.g.*, Cowan, *J. Amer. Oil Chem. Soc.*, 1950, **27**, 493) that this is indeed already known to occur: but, apart from two instances of an early date cited by Cowan (*loc. cit.*, Table III), we have not been able to find unequivocal experimental evidence in the literature of acyl migration effected purely by thermal action. The instances mentioned were (*a*) that a mixture of ethyl benzoate and amyl acetate undergoes an appreciable amount of acyl interchange when heated at 300° for 3—5 hours without a catalyst, and (*b*) that a mixture of beef stearin and soya-bean oil, which melted at 42·5°, underwent a fall in m. p. to 36° after being heated (without catalyst) for 16 hours at 275°.

The *prima facie* possibility, or even likelihood, that such non-catalysed acyl interchange may occur at 300° in the case of glycerides may be considered a reasonable assumption from a comparison with the changes which occur in similar circumstances in the specific polyethenoid groups present in linoleo- or linoleno-glycerides. It is now well established (Steger and van Loon, *Fettchem. Umschau*, 1935, **42**, 217; Bradley and Richardson, *Ind. Eng. Chem.*, 1940, **32**, 963; Mitchell and Kraybill, *ibid.*, 1941, **33**, 764; Paschke and Wheeler, *J. Amer. Oil Chem. Soc.*, 1949, **26**, 278) that the primary change which sets in when such glycerides (in "drying" oils) are heated at 300° is a rearrangement of unconjugated pentadiene (–CH:CH·CH_2·CH:CH–) systems to conjugated dienes. This change, brought about thermally at 300°, can be induced at lower temperatures by the intervention of specific catalysts [nickel (Waterman and van Vlodrop, *J. Soc. Chem. Ind.*, 1936, **55**, 320T; Radlove, Cowan, and Kass, *Ind. Eng. Chem.*, 1946, **38**, 997, 1002) or sulphur dioxide (Waterman and van Vlodrop, *J. Soc. Chem. Ind.*, 1936, **55**, 333T) at 200—220° or at 180° by the action of alkali hydroxide]. It was therefore considered of interest to ascertain definitely whether triglyceride "inter-esterification" or acyl interchange, which can be catalysed by the agents mentioned earlier at temperatures from about 220° downwards, may also proceed by thermal action alone in the neighbourhood of 300°.

Triglycerides containing a mixture of fatty acids (*e.g.*, for simplicity, a mixture of stearic and oleic acids), when prepared at comparatively high temperatures (150° or above), form a mixture the composition of which is not far from that indicated by the theory of probability ("random distribution" of acyl groups amongst the triglyceride molecules). Thus Bhattacharya and Hilditch (*Proc. Roy. Soc.*, 1930, *A*, **129**, 468) showed that the triglycerides produced at 145° by heating glycerol with a slight excess of binary mixtures of different saturated acids with oleic acid, in presence of traces of an aromatic sulphonic acid as catalyst, contained trisaturated glycerides in proportions which followed closely, but not quite identically with, the relation % trisaturated glycerides $\propto$ (% saturated acid)^3. With equimolecular mixtures of stearic and oleic acids, for example, the composition of the triglycerides was approximately 12·5% each of tristearin and triolein, with 37·5% each of oleodistearin and stearodiolein; when

saturated acids were in excess of unsaturated acids the observed percentage of trisaturated glycerides was somewhat greater than that calculated from probability, and conversely. It has since been proved that the mixtures of triglycerides present in natural fatty oils (which are *not* constituted on the lines of " random " or " probability " distribution), and also mixtures of simple triglycerides, when heated for some time at about 200° in presence of a suitable catalyst, undergo acyl rearrangement to a mixture of triglycerides which approaches in composition that calculable from probability considerations and that which is observed in glycerides synthesised from glycerol and fatty acids by esterification at comparable temperatures. Norris and Mattil (*Oil and Soap*, 1946, **23**, 289; *J. Amer. Oil Chem. Soc.*, 1947, **24**, 274) showed that, in presence of stannous hydroxide at 225°, the glycerides of soya-bean oil, of cottonseed oil, or of a mixture of tripalmitin and triolein underwent rearrangement of this nature. Naudet and Desnuelle (*Bull. Soc. chim.*, 1947, [v], **14**, 323) observed that an equimolecular mixture of tristearin and triolein, after being heated for some hours at 205° in presence of a small proportion of sodium methoxide, consisted of a mixture of tristearin 11·3%, oleodistearin 38·6%, stearodiolein 39·2%, and triolein 10·9%.

TABLE I.

Constitution of the (neutral) triglycerides obtained by heating β-oleodistearin at 300°.

	Tristearin, %.	Oleodistearin, %.	Stearodiolein, %.	Triolein, %.
Original oleodistearin	—	99·5	0·5	—
Calc. for " random distribution "	29·7	44·4	22·2	3·7
After 5 hours at 300° (in glass)	17·2	67·7	14·6	0·3
Calc.	(17·2)	67·8	12·9	2·1
After 5 hours at 300° (in silica)	19·9	61·8	18·1	0·2
Calc.	(19·9)	62·7	15·9	2·5
After 10 hours at 300° (in glass)	25·0	54·2	20·2	0·6
Calc.	(25·0)	53·2	18·7	3·1
After 10 hours at 300° (in silica)	27·5	48·1	24·2	0·2
Calc.	(27·5)	48·5	20·6	3·4
After 20 hours at 300° (in silica)	24·1	54·9	19·2	1·8
(Calc.	(24·1)	54·9	18·0	3·0
After 38 hours at 300° (in silica)	27·6	48·3	24·1	—
Calc.	(27·6)	48·4	20·6	3·4

For the purpose of the present work we have studied the behaviour of a single mixed glyceride, β-oleodistearin, when heated at 300° without catalyst under protection of an atmosphere of pure nitrogen. β-Oleodistearin is a natural glyceride present in quantity in a few specific seed fats, from one of which (that of *Garcinia morella*) it was readily isolated in an almost pure condition. The original material, and also the products obtained after heating it at 300°, were investigated by methods similar to those which have been recently described (*J.*, 1950, 3145). In the present instance, however, nearly all of any tristearin present was readily separated from the remaining constituents by reason of its very sparing solubility in ether at room temperature. The specimen of β-oleodistearin employed failed to yield any evidence of the presence of tristearin when submitted to this crystallisation procedure, the analysis indicating that it consisted of 99·5% of oleodistearin accompanied by 0·5% of stearodiolein. Its component fatty acids were stearic 66·5, oleic 33·4, and linoleic 0·1% (wt.). This composition corresponds with a " randomly distributed " glyceride structure (calculated according to probability) of tristearin 29·7, oleodistearin 44·4, stearodiolein 22·2, and triolein 3·7% (wt.).

The composition of the neutral glycerides left after the β-oleodistearin had been heated at 300° for varying periods in Wood's resistance glass or in silica vessels is shown in Table I. Appended to each experimental result is the composition of the oleodistearin, stearodiolein, and triolein proportions, calculated on the assumption that the observed percentage of tristearin had been produced by " random " rearrangement in the proportion of 29·7 parts of tristearin from 100 parts of oleodistearin, the other components having been correspondingly formed by operation of the same principle.

The results in Table I show unequivocally that acyl rearrangement in triglycerides proceeds steadily, if somewhat slowly, at 300° by thermal action alone, that equilibrium is reached in about 10 hours and that the composition of the equilibrium mixture approximates fairly closely to that calculated from probability considerations. Before discussing them in some further detail, however, attention may be directed to the steady but comparatively slow production of free fatty acids which also takes place. This is illustrated in Table II, and it should

perhaps be pointed out that this is the only side reaction which could be detected. Much less discoloration of the glycerides was perceptible than might have been expected. The products after five and ten hours' treatment at 300° were still of only a very slightly darker cream colour than the original, and even after 38 hours at 300° the colour of the neutral glycerides left was not deeper than a clear yellow. Oleo-glycerides are thus of fairly high stability at 300° if contact with oxygen is avoided.

TABLE II.

Production of free fatty acids from β-oleodistearin at 300°.

	Neutral glycerides, %	Free fatty acid, %	Composition of free fatty acids, stearic, %	oleic, %	linoleic, %
After 5 hours at 300° (in glass)	96·3	3·7	65·7	34·3	—
,, 5 ,, 300° (in silica)	95·1	4·9	68·2	30·5	1·3
,, 10 ,, 300° (in glass)	91·6	8·4	57·6	42·4	—
,, 10 ,, 300° (in silica)	88·1	11·9	66·8	32·4	0·8
,, 20 ,, 300° (in silica)	82·9	17·1	67·7	31·4	0·9
,, 38 ,, 300° (in silica)	61·0	39·0	75·5	23·8	0·7

There is a comparatively steady production of free fatty acids at the rate of about 1% per hour at 300°. In four instances the composition of the liberated acids was indistinguishable from that of the original fat, in the remaining two it varied somewhat. The formation of free fatty acid is explicable in the following manner, on the assumption that the acyl interchange is effected by momentary severance of an ester-linkage (either as free radicals, or as a molecule of free acid and a free glyceryl hydroxyl group by the interaction of a molecule of water), followed by instantaneous recombination to the same or a different glyceride ester. At any one instant in any one triglyceride molecule it may be supposed that for the most part only one ester-linkage is concerned in this mechanism, but in a few instances two acyl groups might be simultaneously involved, and in a very few instances all three acyl radicals of one triglyceride molecule might be dissociated at once. In the last case if, as would be expected, the liberated molecule of glycerol (or the free glyceryl radical C_3H_5) were instantly thermally decomposed before it could be re-united with acyl groups, the elements of water necessary for the formation of free acid would arise from this source. This suggested explanation receives some confirmation from the fact that no distearin or monostearin was detectable in the fully-saturated glycerides precipitated from solutions of the products in ether at room temperature: these consisted wholly of tristearin, as indicated by their melting points alone and when mixed with an authentic specimen of tristearin (m. p. 71·3°):

Fully-saturated glycerides isolated from β-oleodistearin after heating at 300°.

	Melting point, alone.	mixed.
After 5 hours at 300° (in glass)	71·6°	71·5°
,, 10 ,, 300° (in silica)	71·7	71·5
,, 20 ,, 300° (in silica)	71·4	71·4

The composition of the neutral glycerides after the heat-treatment presents several other features worthy of some comment. The use of a glass flask was replaced by that of a fused silica container in order to eliminate any possible catalytic effect of alkali in the glass. Actually it appeared that both the acyl interchange and the production of free fatty acid were slightly more pronounced in the fused silica than in the glass vessels.

The accordance between the calculated and the observed proportions of oleodistearin in the products is extremely close: that between corresponding values for stearodiolein and triolein is somewhat less so, the observed proportions of triolein being very small. This was not unexpected since triolein is rather different from other triunsaturated glycerides (such as oleolinoleins, linoleolinolenins, etc.) in that its solubility in acetone or ether is much less than that of those mentioned, and is more nearly comparable with that of dioleoglycerides such as palmito- or stearo-dioleins. Consequently efficient separation of small amounts of triolein from stearodioleins by crystallisation from solvents is a matter of great difficulty.

The maximum production of tristearin observed (27·5%) is some two units per cent. lower than that demanded by the application of the theory of probability: but it is identical with

that shown by the graph (Bhattacharya and Hilditch, *loc. cit.*) connecting the observed proportions of trisaturated glycerides with the proportions of saturated acids in triglycerides prepared by high-temperature esterification of glycerol with saturated–oleic acid mixtures. It may well be that, just as most natural fats do not follow with complete rigidity the operation of " even " distribution indicated by mere arithmetical calculation, the " random " arrangement of mixed triglycerides produced at high temperatures does not wholly conform with that demanded by the purely algebraic application of the theory of probability.

It has been clearly demonstrated by this study, nevertheless, that acyl interchange in mixed triglycerides can be effected merely by heat at temperatures of 300° or thereabouts. In further illustration of this it may be noted that the present oleodistearin concentrates isolated from the products in the course of the crystallisation analyses (cf. Experimental, Table IV) melted indefinitely at various temperatures, all of which were considerably different from that (41·9°) of the original β-oleodistearin :

Oleodistearin concentrate from product after treatment at 300°.	Iodine value.	Component acids, stearic, %.	oleic, %.	M. p.
5 hours (in glass), crystallised fraction D	27·9	67·7	32·4	37—39°
5 ,, (in glass) ,, ,, E	28·8	66·6	33·4	32—36
5 ,, (in silica), ,, ,, C	28·1	67·4	32·6	41—44
5 ,, (in silica), ,, ,, D	28·8	66·6	33·4	38·5—40
10 ,, (in glass), ,, ,, D	29·0	66·4	33·6	25—31
10 ,, (in silica), ,, ,, D	27·9	67·6	32·4	35—39
20 ,, (in silica), ,, ,, C	29·0	66·4	33·6	31—37

These figures suggest that the mono-oleo-glycerides in the products are mixtures of both α- and β-oleodistearins. It is hoped that more detailed study of some of these fractions and their melting and transition points will be undertaken by Dr. M. L. Meara in this laboratory.

Experimental.

β-Oleodistearin was isolated in an almost pure condition by crystallisation of the fat from seeds of *Garcinia morella*, a supply of which was available. The component acids of this fat have been shown by Hilditch and Murti (*J. Soc. Chem. Ind.*, 1941, **60**, 16) to consist almost wholly of stearic and oleic acids, accompanied by small amounts (*ca.* 1% each) of linoleic and palmitic acids. The crude seed-fat (about 400 g.) was crystallised from acetone (4000 ml.) at 0°, and the deposited glycerides recrystallised again under the same conditions; about 120 g. of almost white fat (iodine value 28·9; calc. for oleodistearin 28·6; free fatty acid 0·1%) were obtained which melted sharply at 41·9°.

The component fatty acids of this specimen were determined by spectrophotometric analysis to be stearic 66·5, oleic 33·4, linoleic 0·1% (wt.). The component glycerides were determined by a further series of systematic crystallisations on the lines employed subsequently for the heat-treated products (see below). The oleodistearin (27·6 g.) was first crystallised from ether at 10—12°, and the deposited glycerides (13·0 g.) recrystallised under the same conditions, yielding fractions A and B. The material left in solution (14·6 g.) was crystallised three times from ether at 0°, leaving in solution fractions F, E, and D respectively, fraction C (12·8 g.) being deposited from the final crystallisation at 0°.

The component acids of each fraction were determined from the iodine values combined with spectrophotometric analysis (after alkali-isomerisation) for linoleic acid, which was only detectable in the most soluble fraction F. The consequent composition of the material is shown in Table III.

Thermal Treatment of the Oleodistearin.—The material was heated, either in a small round-bottomed flask of glass (Wood's resistance) or in a large test-tube made of fused silica. In either case an atmosphere of pure nitrogen was maintained over the surface of the melted glyceride and allowed to escape in a slow stream by a vent in the cork inserted in the neck of the apparatus, which was maintained at 300° (±3°)

Table III.

Component glycerides of the oleodistearin used.

	Fractions from ether. A.	B.	C.	D.	E.	F.	Total.
Weight (g.)	1·4	11·6	12·8	0·3	0·3	1·2	27·6
Iodine value	29·1	28·6	28·7	32·4	33·0	30·0	28·9
Glycerides, % (wt.)	5·1	42·0	46·4	1·0	1·1	4·4	100·0
Components acids (% wt.).							
Stearic	66·3	66·7	66·6	62·5	61·7	66·6	66·5
Oleic	33·7	33·3	33·4	37·5	38·3	32·1	33·4
Linoleic	—	—	—	—	—	1·3	0·1
Component glycerides (increments, % wt.).							
" Oleo "-distearin	5·0	42·0	46·3	0·9	0·9	4·4	99·5
Stearo-di" olein "	0·1	—	0·1	0·1	0·2	—	0·5

TABLE IV.

Glyceride fractions separated by crystallisation after heating of oleodistearin at 300°.

Fraction.	G.	%	Iodine value.	Free fatty acid (%).	Component fatty acids present, %. stearic.	oleic.	linoleic.
			After 5 hours' heating at 300° (in glass).				
A	4·31	16·2	1·6	—	98·1	1·9	—
B	0·89	3·3	30·7	0·8 *	64·4	35·6	—
C	1·43	5·4	22·7	—	73·7	26·3	—
D	1·66	6·2	27·9	0·3 *	67·6	32·4	—
E	7·76	29·2	28·8	0·3 *	66·6	33·4	—
F	5·61	21·1	32·7	1·8 *	62·1	37·9	—
G	1·35	5·1	37·1	21·5	52·2 71·8	46·9 28·2	0·9 (neutral glycerides) — (free acids)
H	2·17	8·2	48·8	10·4	41·0 75·2	58·4 24·8	0·6 (neutral glycerides) — (free acids)
I	1·40	5·3	63·7	24·6	29·6 27·5	69·0 72·5	1·4 (neutral glycerides) — (free acids)
	26·58	100·0					
			After 5 hours' heating at 300° (in silica).				
A	1·64	17·2	2·4	—	97·2	2·8	—
B	0·64	6·7	16·2	0·6 *	81·2	18·8	—
C	1·16	12·2	28·1	—	67·4	32·6	—
D	2·82	29·7	28·8	0·2 *	66·6	33·4	—
FA	0·47	4·9	30·0	98·0	68·2	30·5	1·3 (free acids)
E	2·06	21·7	41·7	—	51·6	48·4	—
F	0·72	7·6	58·5	—	32·3	64·8	2·9
	9·51	100·0					
			After 10 hours' heating at 300° (in glass).				
A	6·84	21·7	1·3	—	98·5	1·5	—
B	5·58	17·7	25·2	0·4 *	70·8	29·2	—
C	2·39	7·6	32·4	1·2 *	62·4	37·6	—
FA	2·58	8·2	38·2	100·0	57·6	42·4	— (free acids)
D	5·99	19·0	29·0	—	66·4	33·6	—
E	3·19	10·1	37·0	—	57·1	42·9	—
F	1·60	5·0	53·7	—	37·7	62·3	—
G	3·37	10·7	59·3	—	31·6	66·9	1·5
	31·54	100·0					
			After 10 hours' heating at 300° (in silica).				
A	4·10	23·1	2·0	0·2 *	97·7	2·3	—
B	1·76	9·9	21·8	—	74·7	25·3	—
C	2·08	11·7	30·9	5·6 *	62·0	38·0	—
D	2·36	13·3	27·9	0·3 *	67·6	32·4	—
FA	1·99	11·2	30·6	100·0	66·8	32·4	0·8 (free acids)
E	2·04	11·5	35·0	—	59·4	40·6	—
F	1·74	9·8	53·2	—	38·3	61·7	—
G	1·15	6·5	58·3	—	35·4	63·2	1·4
H	0·53	3·0	61·8	—	30·9	65·9	3·2
	17·75	100·0					
			After 20 hours' heating at 300° (in silica).				
A	2·37	21·9	2·6	—	97·0	3·0	—
B	1·10	10·1	27·1	5·6 *	66·7	33·3	—
FA	1·79	16·5	29·9	100·0	67·7	31·4	0·9 (free acids)
C	2·51	23·1	29·0	—	66·4	33·6	—
D	0·95	8·8	42·7	—	50·5	49·5	—
E	1·35	12·4	43·1	—	51·1	48·2	0·7
F	0·78	7·2	64·8	—	26·5	71·9	1·6
	10·85	100·0					
			After 38 hours' heating at 300° (in silica).				
A	1·81	16·6	0·3	0·7 *	99·7	0·3	—
B	0·90	8·3	27·1	—	68·6	31·4	—
FA	4·26	39·3	22·0	97·0	75·5	23·8	0·7 (free acids)
C	3·88	35·8	39·5	2·1	53·1	43·8	3·1
	10·85	100·0					

* Small proportions of (saturated) acids deposited with fractions of the more sparingly soluble glycerides are calculated as stearic acid.

TABLE V.

Composition of glyceride fractions and, therefrom, of the glyceride mixtures produced at 300°.

Fraction.	Proportion, %.	Neutral glycerides present, tristearin.	oleodistearins.	stearodioleins.*	triolein.*	Free fatty acids, stearic.	oleic.*
After 5 hours' heating of β-oleodistearin at 300° (in glass).							
A	16·2	15·3	0·9	—	—	—	—
B	3·3	—	3·1	0·2	—	Trace	—
C	5·4	1·1	4·3	—	—	—	—
D	6·2	0·2	6·0	—	—	Trace	—
E	29·2	—	29·1	—	—	0·1	—
F	21·1	—	17·8	2·9	—	0·4	—
G	5·1	—	2·3	1·7	—	1·0	0·1
H	8·2	—	1·7	5·7	—	0·6	0·2
I	5·3	—	—	3·5	0·5	0·4	0·9
Totals	100·0	16·6	65·2	14·0	0·5	2·5	1·2
After 5 hours' heating of β-oleodistearin at 300° (in silica).							
A	17·2	15·7	1·5	—	—	—	—
B	6·7	2·9	3·8	—	—	Trace	—
C	12·2	0·3	11·9	—	—	—	—
D	29·7	—	29·6	—	—	0·1	—
FA	4·9	—	0·1	Trace	—	3·3	1·5
E	21·7	—	11·9	9·8	—	—	—
F	7·6	—	—	7·4	0·2	—	—
Totals	100·0	18·9	58·8	17·2	0·2	3·4	1·5
After 10 hours' heating of β-oleodistearin at 300° (in glass).							
A	21·7	20·7	1·0	—	—	—	—
B	17·7	2·2	15·4	—	—	0·1	—
C	7·6	—	6·6	0·9	—	0·1	—
FA	8·2	—	—	—	—	4·7	3·5
D	19·0	—	18·8	0·2	—	—	—
E	10·1	—	7·2	2·9	—	—	—
F	5·0	—	0·7	4·3	—	—	—
G	10·7	—	—	10·2	0·5	—	—
Totals	100·0	22·9	49·7	18·5	0·5	4·9	3·5
After 10 hours' heating of β-oleodistearin at 300° (in silica).							
A	23·1	21·5	1·6	—	—	*Trace*	—
B	9·9	2·4	7·5	—	—	—	—
C	11·7	—	9·5	1·6	—	0·6	—
D	13·3	0·3	12·9	—	—	0·1	—
FA	11·2	—	—	—	—	7·5	3·7
E	11·5	—	9·0	2·5	—	—	—
F	9·8	—	1·5	8·3	—	—	—
G	6·5	—	0·4	6·1	—	—	—
H	3·0	—	—	2·8	0·2	—	—
Totals	100·0	24·2	42·4	21·3	0·2	8·2	3·7
After 20 hours' heating of β-oleodistearin at 300° (in silica).							
A	21·9	19·9	2·0	—	—	—	—
B	10·1	Trace	9·5	—	—	0·6	—
FA	16·5	—	—	—	—	11·2	5·3
C	23·1	—	22·9	0·2	—	—	—
D	8·8	—	4·5	4·3	—	—	—
E	12·4	—	6·6	5·8	—	—	—
F	7·2	—	—	5·7	1·5	—	—
Totals	100·0	19·9	45·5	16·0	1·5	11·8	5·3
After 38 hours' heating of β-oleodistearin at 300° (in silica).							
A	16·6	16·3	0·2	—	—	0·1	—
B	8·3	0·5	7·8	—	—	—	—
FA	39·3	—	0·7	0·5	—	28·8	9·3
C	35·8	—	20·8	14·2	—	0·4	0·4
Totals	100·0	16·8	29·5	14·7	—	29·3	9·7

* Small amounts of linoleic acid or glycerides, when present, included with oleic.

in an aluminium air-bath which completely surrounded all except the top of the neck of the glass or silica vessel. Heating was applied in different experiments for 5, 10, 20, and 38 hours.

Examination of the Products.—These were first crystallised from 10% solution in ether at room temperature (usually 12—18°); insoluble matter (mainly tristearin) was at once deposited, and was recrystallised under the same conditions to give the two least soluble glyceride fractions A and B. The material left in solution in ether was then crystallised once or twice from acetone at room temperature, concentrates rich in oleodistearin being deposited. The acetone-soluble compounds were recovered and, at this stage, were in most instances dissolved in ether and neutralised by washing with dilute aqueous potassium hydroxide solution in order to remove the free fatty acid which had been produced (fractions lettered FA). Neutralisation of the total product was impracticable owing to the sparing solubility in ether of the tristearin present. [In one instance (5 hours at 300° in glass) this procedure was not followed, the free acidity being determined in each fraction, and the composition of the free acids being separately determined in each case.] Finally, in all cases, crystallisation of the more soluble remaining material (whether neutralised or otherwise) was continued from acetone at successively lower temperatures from 0° to −15° until as much resolution as possible of stearodioleins from oleodistearins or triolein had been accomplished. The crystallisation procedure varied in details according to the nature of the product, and Table IV gives a condensed summary of the proportions, characteristics, and composition of each of the glyceride fractions isolated from each of the heated products. The fatty acids in each fraction were determined from their iodine values in conjunction with spectrophotometric data for any linoleic or conjugated diene acid present. Diene acids were only evident in the most soluble or (at most) two most soluble glyceride fractions from each product. It was noticed in all cases that these acids were very largely in the conjugated form: thus, for instance, the acids from the most soluble fraction H of the product heated at 300° for 10 hours in a fused silica tube showed $E^{1\%}_{1\,cm.}$ (at 234 mμ.) 26 (unisomerised) and 34 (after alkali-isomerisation).

Occasionally, in some of the earlier crystallisations of a product, very small proportions of free saturated acid separated out with the oleodistearin and tristearin concentrates; these were calculated as free stearic acid (Table IV).

The deduced increments of tristearin, oleodistearins, stearodioleins, triolein, and free stearic or oleic acid in each glyceride fraction (and therefrom the proportion of each in the six products examined) are shown in Table V. For the purpose of the glyceride constitution the small amounts of linoleic acid, when present, have been included with the oleic acid in this table, which therefore, strictly speaking, shows the relative proportions of stearic and unsaturated ("oleo"-)glycerides of the different types. The figures in Table V refer to compositions by weight, since in view of the small difference in molecular weights of stearic and oleic acids it is here unnecessary to consider separately the molecular proportions of the components of the mixtures.

We thank the Colonial Products Research Council for authority to publish the above results and for grants to two of us (C. B. and R. V. C.) during the course of this study.

THE UNIVERSITY, LIVERPOOL. [*Received, February 5th*, 1951.]

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268. *The Unsaponifiable Matter of Butter Fat. Part I.*

By ISOBEL M. MORICE.

Chromatography has shown the unsaponifiable matter of butter fat to be extremely complex. From it have been isolated the triterpene lanosterol, previously obtained only from wool fat and yeast, and small amounts of four other colourless crystalline compounds not hitherto known to occur in butter. Compound A, detected by Morton and Heilbron (*Biochem. J.*, 1930, **24**, 870) and reported as an unidentified substance with an absorption maximum at 272 mμ., has m. p. 108° and probable formula $C_{19}H_{16}O$; compounds B (m. p. 80°), C (m. p. 65°), and D (m. p. 38°) have probable formulæ $C_{27}H_{56}O$, $C_{14}H_{28}O_2$, and $C_{14}H_{26}O$ respectively.

THE unsaponifiable matter of butter is known to contain cholesterol (Kreis and Wolf, *Chem.-Ztg.*, 1898, **2**, 805), β-carotene (Gillam and El Ridi, *Biochem. J.*, 1937, **31**, 251), and squalene (Fitelson, *J. Assoc. Off. Agric. Chem.*, 1943, **26**, 506), which have been isolated from it, vitamin A (Morton and Heilbron, *Biochem. J.*, 1930, **24**, 870), kryptoxanthin, and lycopene (Gillam and Heilbron, *ibid.*, 1935, **29**, 834), which have been detected by their absorption spectra, and vitamin D (Kon and Booth, *ibid.*, 1934, **28**, 111) which biological tests have shown to be present.

The purpose of this investigation was to determine if the unsaponifiable matter of butter fat contained any other substances. Accordingly it was separated into three fractions by its solubility in methanol at 50° and −26°, and each fraction further divided by chromatography. Adsorption of the fraction soluble in methyl alcohol at −26° on alumina gave a number of

sub-fractions. Re-adsorption of these, followed by crystallisation, showed that the material adsorbed immediately below cholesterol was a colourless substance crystallising from methanol in soft needles, m. p. 138—139°, but forming a jelly with light petroleum. This compound formed an acetate and a benzoate, and the melting points of these, together with its slow precipitation by digitonin and the yellow colour with a green fluorescence given by the Liebermann–Burchard reagent (Burchard, *Chem. Zentr.*, 1890, I, 25) led to the supposition that it was lanosterol. Wieland, Pasedach, and Ballauf (*Annalen*, 1937, **529**, 68) report that cryptosterol, which has since been proved by Ruzicka, Denss, and Jeger (*Helv. Chim. Acta*, 1945, **28**, 759) to be identical with lanosterol, gives a yellow colour with the Liebermann–Burchard reagent.

The melting points and specific rotations of our alcohol, and that from wool fat, and of their acetates and benzoates, are similar (see Table I which gives also data recorded for

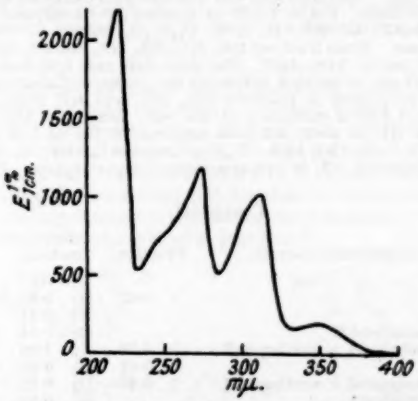
TABLE I.

	Alcohol.		Acetate.		Benzoate.		
Source.	M. p.	$[\alpha]_D$.	M. p.	$[\alpha]_D$.	M. p.	$[\alpha]_D$.	Reference.
Butter fat ...	138—139°	+59·1°	127—128°	+59·0°	191—192°	+76·3°	This paper
Wool fat ...	138—139	61·6	125—127	61·2	191—192	76·9	,,
Yeast	138—139·5	60·7	130—131	65·3	190—191	70·5	*a*, *b*
Wool fat ...	138—139	62·3	128—129	64·5	191·5	74·5	*b*, *c*

(*a*) Wieland, Pasedach, and Ballauf, *loc. cit.* (*b*) Ruzicka, Denss, and Jeger, *loc. cit.* (*c*) Windaus and Tschesche, *Z. physiol. Chem.*, 1930, **190**, 51.

cryptosterol and lanosterol); mixed melting points gave no depression. Thus it appears certain that this alcohol occurring in butter fat is lanosterol.

From the absorption spectrum of the unsaponifiable matter of butter Morton and Heilbron (*loc. cit.*) reported the presence of an unidentified substance giving a maximum at 272 mμ. This has now been isolated and provisionally named compound A. It was found on the alumina column below lanosterol, has m. p. 108°, and in ethanol absorbs strongly at 272·5 mμ. with other maxima at 220, 310, and 348 mμ. (see figure). It is highly unsaturated to tetranitromethane, and appears to have the formula $C_{19}H_{14}O$.



Ultra-violet absorption spectrum of compound A in 95% ethanol.

Three other crystalline substances, provisionally named B, C, and D, not previously known in butter have been isolated. They appear all to be saturated. The probable formulæ are $C_{27}H_{44}O$, $C_{14}H_{28}O_2$, and $C_{14}H_{28}O$, respectively. The four compounds, A, B, C, and D, occur in very small quantities and are not yet fully characterised. Further work on them is in progress.

EXPERIMENTAL.

(M. p.s are uncorrected. Specific rotations are in chloroform. The light petroleum boiled at 50—60°. The analyses are by Mr. B. R. Thomas, Dominion Laboratory, and Dr. T. S. Ma, University of Otago.)

The Unsaponifiable Matter of Butter Fat.—Butter fat (4 kg.) was saponified with 0·5*N*-alcoholic potassium hydroxide (40 l.), and the unsaponifiable matter extracted with ether according to the method

recorded in *The Analyst*, 1933, **58**, 203. The unsaponifiable matter (21 g.) was divided into fractions: I, insoluble in 1050 ml. of methanol at 50° (6·2%); II, soluble in methanol at 50°, insoluble at −26° (64·5%); and III, soluble at −26° (29·3%).

Fraction I (1·3 g.), dissolved in light petroleum (125 ml.), was adsorbed on a column of alumina (55 g.; 23 × 1·8 cm.). The column was eluted successively with light petroleum (500 ml.), benzene (450 ml.), ether (300 ml.), and ethanol (350 ml.) in 50 ml. portions. Four fractions, 0·06, 0·50, 0·09, and 0·65 g., in decreasing order of adsorbability, were obtained. The second fraction, in light petroleum, deposited crystals of cholesterol (147 mg.), m. p. 148—149°, which was identified by mixed melting point with authentic cholesterol. Some colourless waxy crystals (50 mg.), m. p. 63—65°, were obtained from the fourth fraction but did not appear to be pure.

Fraction II (13·5 g.), dissolved in benzene (280 ml.), was adsorbed on alumina (140 g.; 28 × 2·5 cm.). The column was eluted successively with benzene (4350 ml.), ether (2250 ml.), and benzene–ethanol (2250 ml.) in 150 ml. portions. The five fractions obtained, in decreasing order of adsorbability, are shown in Table II. Fraction 2 in acetone gave cholesterol (7·87 g.), m. p. 149—150°. Fraction 3 in acetone gave *compound B* (32 mg.) as colourless crystals, 79—80° (Found: C, 81·7; H, 14·3. $C_{27}H_{44}O$ requires C, 81·7; H, 14·2%), giving no colour with tetranitromethane. Fraction 4 in benzene–methanol gave 6 mg. of somewhat impure β-carotene which when pure melted at 182—183°, did not depress the m. p. of authentic β-carotene, and had an absorption spectrum identical with that of authentic β-carotene. From fraction 5 in acetone were obtained colourless crystals (40 mg.), m. p. 60—61° (Found: C, 85·3; H, 14·8. $C_{28}H_{44}$ requires C, 85·2; H, 14·8%), giving no colour with tetranitromethane. Although the m. p. is sharp it seems doubtful whether this is one hydrocarbon only.

TABLE II.

Fraction.	Wt. (g.).	Compound present.	Fraction.	Wt. (g.).	Compound present.
1	0·30	—	4	0·14	β-Carotene
2	10·64	Cholesterol	5	1·98	Hydrocarbon mixture, m. p. 61°
3	0·44	Compound B			

Fraction III (6·2 g.), dissolved in light petroleum (130 ml.), was adsorbed on alumina (130 g.; 26 × 2·5 cm.). The column was divided into nine portions, of which the three upper were eluted with 95% ethanol and the six lower with 95% ethanol and light petroleum.

Fractions 4—8 were dissolved in light petroleum and separately re-adsorbed on alumina. Fraction 3 in light petroleum was re-adsorbed on calcium oxide. Fractions 1 and 2 were dissolved in chloroform and separately re-adsorbed on alumina. In several cases the highest sub-fraction was added to the fraction above before re-adsorption, and the lowest sub-fraction added to the highest remaining sub-fraction of the fraction below. The fractions and sub-fractions obtained are shown in Table III in decreasing order of adsorbability. Fraction 1(3) in acetone gave *compound C* (44 mg.) as colourless crystals, m. p. 64—65° (Found: C, 73·1; H, 12·8. $C_{14}H_{28}O_2$ requires C, 73·6; H, 12·4%), giving no colour with tetranitromethane. From fractions 1(4), 2(1), 2(2), 2(3), and 3(2) light petroleum or methanol gave cholesterol (340 mg.), m. p. 146—147°. Fractions 1(4) and 2(1) had absorption spectra with maxima at 424, 445, and 472 mμ. in ethanol, indicating the presence of small amounts of a xanthophyll. Vitamin A was shown to be present in fractions 2(3), 3(2), and 4(1) which gave typical vitamin-A absorption curves in ethanol with a maximum at 324 mμ. Lanosterol and *compound A* are further described below. Fraction 8(1) in methanol gave *compound D* (40 mg.) as colourless crystals, m. p. 37—38° (Found: C, 79·2, 79·3; H, 13·1, 13·2. $C_{14}H_{28}O$ requires C, 79·2; H, 13·3%), showing no colour with tetranitromethane. Fraction 8(2) in benzene–methanol gave approx. 3 mg. of β-carotene, m. p. 182—183°.

TABLE III.

Fraction.		Sub-fraction.		Compounds present.	Fraction.		Sub-fraction.		Compounds present.
	G.		G.			G.		G.	
1	0·92	(1)	0·06	—	4	0·62	(1)	0·59	Lanosterol, vitamin A
		(2)	0·10	—			(2)	0·15	Lanosterol
		(3)	0·50	Compound C			(3)	0·14	Lanosterol
		(4)	0·12	Cholesterol, a xanthophyll	5	0·78	(1)	1·06	Lanosterol
		(5)	0·02	—	6	0·42	(1)	0·18	Compound A
2	1·37	(1)	0·54	Cholesterol, a xanthophyll	7	0·20	(1)	0·12	Compound A
		(2)	0·43	Cholesterol			(2)	0·02	—
		(3)	0·39	Cholesterol, vitamin A	8	0·28	(1)	0·20	Compound D
		(4)	0·03	—			(2)	0·09	β-Carotene
3	0·56	(1)	0·11	—	9	1·06	—	—	—
		(2)	0·27	Cholesterol, lanosterol, vitamin A					

Lanosterol.—From fractions 3(2), 4(1, 2, 3), and 5(1) of fraction III was obtained a colourless substance (183 mg.) crystallising in rosettes of soft needles (from methanol), m. p. 138—139°, $[\alpha]_D^{21}$ +59·1° (*l*, 0·5; *c*, 1·29) (Found: C, 84·1, 83·6; H, 11·7, 11·9. Calc. for $C_{30}H_{50}O$: C, 84·5; H, 11·8%). The Liebermann–Burchard reagent gave a yellow colour with a green fluorescence. Digitonin gave a precipitate after approx. one hour.

The substance was acetylated by warm pyridine–acetic anhydride, and the product was precipitated and after two crystallisations (methanol) yielded shining prisms, m. p. 127—128°, $[\alpha]_D^{18}$ +59·0° (*l*, 0·5;

c, 1·36) (Found : C, 82·1; H, 11·6. Calc. for $C_{32}H_{52}O_4$: C, 82·0; H, 11·2%). Hydrolysis of the acetate with 0·3N-alcoholic potassium hydroxide gave the original alcohol, m. p. 138—139°.

The benzoate, formed by pyridine–benzoyl chloride, crystallised from acetone as rosettes of soft shining needles, m. p. 191—192°, $[\alpha]_D^{14}$ +76·3° (*l*, 0·5; *c*, 2·33) (Found : C, 83·4; H, 10·2. Calc. for $C_{37}H_{54}O_2$: C, 83·7; H, 10·3%). Hydrolysis with 0·5N-alcoholic potassium hydroxide gave the original alcohol, m. p. 138—139°.

Lanosterol from Wool Fat.—Two adsorptions of the unsaponifiable matter of wool fat on alumina yielded lanosterol, m. p. 138—139°, $[\alpha]_D^{15}$ +61·6° (*l*, 0·5, *c*, 1·30). Lanosteryl acetate formed prisms (from methanol), m. p. 126—128°, $[\alpha]_D^{16}$ 61·2° (*l*, 0·5, *c*, 1·50). Lanosteryl benzoate crystallised from acetone–methanol in rosettes of soft needles, m. p. 191—192°, $[\alpha]_D^{14}$ +76·9° (*l*, 0·5, *c*, 2·08).

Compound A.—Fractions 6(1) and 7(1) of fraction III, dissolved in light petroleum, gave colourless prismatic needles (40 mg.), m. p. 107·5—108° (Found : C, 87·6, 87·6; H, 6·2, 6·2; *M* (Rast), 232. $C_{13}H_{16}O$ requires C, 87·7; H, 6·2%; *M*, 260). The substance gives a blue fluorescence when dissolved in methanol or ethanol but none in light petroleum. With tetranitromethane a brown colour is obtained. The ultra-violet absorption curve in 95% ethanol determined with a Beckman spectrophotometer has maxima at 220, 272·5, and 310 mμ. and a smaller one at 348 mμ. ($E_{1\,cm}^{1\%}$ = 2225, 1180, 1021, and 190 respectively). The compound was not acetylated by ordinary means, neither did it form an oxime.

FATS RESEARCH LABORATORY,
DEPARTMENT OF SCIENTIFIC AND INDUSTRIAL RESEARCH,
WELLINGTON, NEW ZEALAND.

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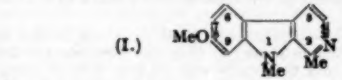
269. *The Chemistry of the* Mitragyna *Genus. Part II. Synthesis of 7-Methoxy-2-methyl- and 7-Methoxy-1 : 2-dimethyl-β-carboline.*

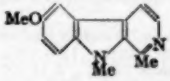
By J. W. COOK, J. D. LOUDON, and P. MCCLOSKEY.

5-Methoxyindole and its 1-methyl derivative have been converted *via* the corresponding derivatives of gramine and tryptophan into 7-methoxy-2-methyl- (III) and 7-methoxy-1 : 2-dimethyl-β-carboline (II). Of these two end-products, the latter (II) was also prepared from the former (III) and was shown, by direct comparison, to be distinct from the base, $C_{14}H_{14}ON_2$, obtained by Ing and Raison (*J.*, 1939, 986) from degradation of mitragynine.

By distilling mitragynine from zinc dust Ing and Raison (*J.*, 1939, 986) obtained a base, $C_{14}H_{14}ON_2$, which contained one methoxyl group, one methylimino-group and one reactive methylene group (*p*-nitrobenzylidene derivative). Despite highly significant similarities it was shown conclusively that this base was not identical with *ind-N*-methylharmine (I) nor—as was indeed less likely—with the isomeric *pyr-N*-methylharmine. The possibility remains that the base is a β-carboline derivative substituted in a manner different from (I). Partly with the object of preparing the compound (II) for specific comparison and partly with the more general purpose of making available close analogues of harmine, we have now synthesised a number of harman derivatives methoxylated at position 7.



(I.)



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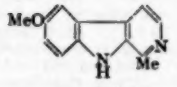
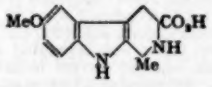
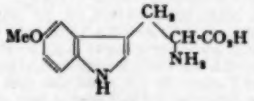


(III.)



(IV.)



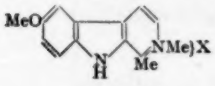
(V.)

Späth and Lederer (*Ber.*, 1930, **63**, 2102) have already described a synthesis of 7-methoxy-2-methyl-β-carboline (III), which proceeds from *p*-methoxyphenylhydrazine and the diethyl acetal of γ-amino-*n*-butaldehyde to 5-methoxytryptamine and its *N*-acetyl derivative, the latter being cyclised and the resulting dihydrocarboline dehydrogenated. We have preferred the alternative " gramine method " of synthesis with 5-methoxytryptophan (V) as intermediate. 5-Methoxygramine (cf. Bell and Lindwall, *J. Org. Chem.*, 1948, **18**, 547) was condensed with ethyl sodio-acetamidomalonate in presence of methyl sulphate according to the procedure of

Albertson, Archer, and Suter (*J. Amer. Chem. Soc.*, 1945, **67**, 36) and the product was hydrolysed first (with decarboxylation) to α-acetamido-β-(5-methoxy-3-indolyl)propionic acid and then to the trytophan (V). Acetaldehyde condensed smoothly with (V) in aqueous solution at ordinary temperature, the tetrahydrocarboline-4-carboxylic acid (IV) crystallising as the reaction progressed. This acid appeared to homogeneous but the mother-liquor contained traces of a by-product which may represent the second of the two possible (±)-forms. Dehydrogenation and simultaneous decarboxylation of (IV), yielding (III), were effected by heating a solution of the acid and potassium dichromate in aqueous acetic acid.

Following the principle by which Iyer and Robinson (*J.*, 1934, 1635) prepared *ind*-*N*-methylharmine from harmine, the base (III) was converted *via* the methosulphate (VI; X = $MeSO_4$) into the methohydroxide (VI; X = OH) whence, by heating to form the anhydronium base (VII) and subsequent addition of methyl iodide, there was obtained 7-methoxy-1 : 2 : 3-trimethyl-β-carbolinium iodide (VIII). When this salt was heated at 300—320° methyl iodide was eliminated and 7-methoxy-1 : 2-dimethyl-β-carboline (II) was produced.

Confirmation of the structure assigned to this product was next sought in an alternative but similar synthesis in which methylation of the indole nitrogen was effected at an early stage. The requisite 5-methoxy-1-methylindole (IX) was prepared by two methods, namely (*a*) by thermal decomposition of 5-methoxy-1-methylindole-2-carboxylic acid and (*b*) together with a small quantity of the corresponding indoline (cf. Julian and Printy, *J. Amer. Chem. Soc.*, 1949, **71**, 3206) by reducing 5-methoxy-1-methyloxindole with lithium aluminium hydride. Both methods afforded the indole (IX) as a well-defined crystalline substance and its previous description as an oil (Bell and Lindwall, *loc. cit.*) is thereby amended. The subsequent stages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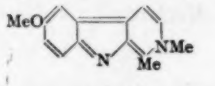
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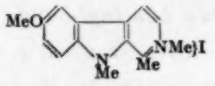
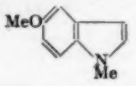

(VIII.)


(IX.)

of the synthesis—through the 5-methoxy-1-methyl derivatives of gramine and tryptophan to the *ind*-*N*-methyl derivatives of (IV) and (III)—followed with minor variations on the lines described for (III) and afforded the product (II) identical in all respects with that obtained by the first method of synthesis.

Through the kindness of Dr. H. R. Ing, whom we warmly thank for placing his specimens at our disposal, direct comparison between the mitragynine degradation product and the base (II) was made possible. This comparison, which was extended to include the picrates and *p*-nitrobenzylidene derivatives, conclusively showed that the respective compounds of the two series are not identical. We hope to compare the degradation product with other harman derivatives of which the syntheses are now in hand.

Experimental.

M. p.s are corrected unless otherwise stated.

5-Methoxyindole was prepared from 5-methoxy-2-nitrotoluene (Cook, Dickson, Ellis, and Loudon, *J.*, 1949, 1074) *via* 5-methoxyindole-2-carboxylic acid as described by Blaikie and Perkin (*J.*, 1924, **125**, 296).

3-Dimethylaminomethyl-5-methoxyindole (*5-Methoxygramine*).—Acetic acid (11·5 c.c.) was added to aqueous dimethylamine (33%; 11·5 c.c.), cooled in a freezing mixture, so that the temperature did not exceed 5°. Formalin (37%; 5·75 c.c.) was then added and the whole was poured, with shaking, into 5-methoxyindole (11·3 g.). Heat was evolved and the resulting light-brown solution was set aside at room temperature for 20 hours, during which some deposition occurred. The mixture was poured into aqueous sodium hydroxide (10%; 200 c.c.) and after 2 hours at 0° the solid was collected, washed with water, powdered, and treated with N-hydrochloric acid (200 c.c.) and ether (50 c.c.). After being freed from some insoluble material the solvent layers were separated, and the aqueous layer was washed with ether (30 c.c.) and was just made alkaline whereby a crude initial precipitate was formed and could be removed by adherence to a stirring rod. Subsequent addition of dilute alkali to the mother-liquor afforded 5-methoxygramine (12·2 g.) as almost white needles of m. p. 124—125° (from benzene) (Bell and Lindwall, *loc. cit.*, give m. p. 127·5—128°) (Found: C, 70·55; H, 7·4; N, 13·8. Calc. for $C_{12}H_{16}ON_2$: C, 70·6; H, 7·8; N, 13·7%). The *picrate* formed amber-coloured prisms, m. p. 164—165°, from benzene–ethanol (Found: C, 49·8; H, 4·7; N, 15·9. $C_{18}H_{19}ON_5C_6H_3O_7N_3$ requires C, 49·9; H, 4·4; N, 16·2%); Wieland and Hsing (*Annalen*, 1936, **526**, 188) give m. p. 168°, without analytical results.

Ethyl α-Acetamido-α-carbethoxy-β-(5-methoxy-3-indolyl)propionate.—Ethyl acetamidomalonate (11·0 g.) was added with mechanical stirring and rigid exclusion of moisture to a cold solution of sodium ethoxide (from 1·15 g. of sodium) in dry ethanol (100 c.c.). 5-Methoxygramine (10·2 g.) was then added, followed, when dissolution was complete, by gradual addition of methyl sulphate (8·3 c.c.) during 25 minutes. The rise in temperature, incurred in the last step, was controlled at 40° (thermometer bulb in reaction

mixture) by occasional external cooling. The mixture was then stirred for 1 hour and left overnight at room temperature. The solid resulting from addition to water (300 c.c.) and cooling in ice (1 hour), was collected, washed with water, and dissolved in benzene (150 c.c.), the solution being washed with N-hydrochloric acid (3 × 50 c.c.), again with water, dried, and concentrated under reduced pressure. The residual glass-like mass was dissolved in ethanol and readily afforded the solid *ester* (17·1 g.) when the solution was poured into cold water. The ester in this form was sufficiently pure for subsequent experiments but was obtained as colourless needles or rods, softening at 126°, m. p. 128—129°, from ethanol–water (1 : 1) (Found: C, 60·7; H, 6·2; N, 7·1. $C_{15}H_{14}O_4N_2$ requires C, 60·6; H, 6·4; N, 7·45%).

α-Acetamido-β-(5-methoxy-3-indolyl)propionic Acid.—The above ester (18·8 g.) was heated under reflux for 1½ hours with a solution of sodium hydroxide (8 g.) in water (80 c.c.). The filtered solution was cooled in ice and acidified, affording a reddish oil which solidified overnight at 0°. The powdered, washed, and air-dried solid (14·6 g.)—probably the malonic acid derivative—had m. p. 156—160° (efferv.) and slowly acquired a purplish colour on exposure to air and light. This acid (14 g.), when heated under reflux with water (100 c.c.), dissolved with gradual evolution of carbon dioxide which was apparently complete after 6 hours. On cooling, *α-acetamido-β-(5-methoxy-3-indolyl)propionic acid* separated as an oil which solidified overnight to a mixture of a hydrated and an anhydrous form. The *hydrate*, colourless rods of m. p. 115—120° (efferv.) from water (Found: C, 57·0; H, 6·2; N, 9·3. $C_{14}H_{16}O_4N_2.H_2O$ requires C, 57·1; H, 6·1; N, 9·5%), resolidified on continued heating and re-melted at 182—183°, *i.e.*, at the m. p. of the anhydrous form which, as small warty nodules, sometimes accompanies the hydrate from aqueous solution and usually changes to the hydrate on recrystallisation. A sample of the hydrate after being heated at 120—125°/18 mm. for 1 hour until effervescence ceased gave the analytical figures: C, 61·1; H, 6·1 ($C_{14}H_{16}O_4N_2$ requires C, 60·9; H, 5·8%). A persistent colour in the crude hydrate was best removed by shaking the hot filtered aqueous solution until the oil which formed began to solidify, whereupon rapid filtration gave an almost colourless solution and a colourless second crop.

α-Amino-β-(5-methoxy-3-indolyl)propionic Acid (*5-Methoxytryptophan*) (V).—A solution of the foregoing acid (2·5 g.) in 10% aqueous sodium hydroxide (25 c.c.) was heated at 100° for 6 hours before being cooled and treated dropwise with acetic acid. Gelatinous silica separated during this last stage. When 2·8 c.c. of acetic acid had been added and the solution was still slightly alkaline, the product suddenly separated as a fine crystalline precipitate which was collected, washed with cold water, dissolved in hot ethanol–water (1 : 1; 50 c.c.), and filtered from silica. Concentration of the filtrate, preferably under reduced pressure, gave 5-methoxytryptophan (1·13 g.), and a further quantity (0·4 g.) was obtained from the combined reaction—and mother—liquors. These were made faintly acid with acetic acid, then slightly alkaline with aqueous ammonia, and concentrated almost to dryness. The residue was dissolved in hot ethanol–water (1 : 1; 10 c.c.), the cooled solution was filtered from sodium acetate, and the filtrate was seeded. *5-Methoxytryptophan* formed slender, colourless rods, m. p. 254—256° (decomp.) with previous softening at 245°, from ethanol–water (1 : 1). For analysis the compound was dried at 100°/15 mm. for 3½ hours over phosphoric oxide (Found: C, 61·3; H, 6·2; N, 11·8. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·0; N, 12·0%).

2 : 3 : 4 : 5-*Tetrahydro-7-methoxy-2-methyl-β-carboline-4-carboxylic Acid* (IV).—5-Methoxytryptophan (0·5 g.) was dissolved in warm water (50 c.c.), and the solution was rapidly cooled and treated with freshly distilled acetaldehyde (1 c.c.). After 3 hours at room temperature the mixture was gently warmed on the water-bath for an hour, cooled and left overnight at 0°. The crystalline product, augmented by a small second crop (total, 0·48 g.) from the concentrated mother-liquor, afforded the *acid* as masses of tiny needles, m. p. *ca.* 240—245° with sintering at 235°, from hot water (charcoal) (Found: C, 56·7; H, 6·8; N, 9·3. $C_{14}H_{16}O_3N_2.2H_2O$ requires C, 56·8; H, 6·8; N, 9·5%). When the combined mother-liquors from several preparations were evaporated and the residue was crystallised from water, a first crop, consisting of the above product, was followed by a small second crop of material which had m. p. 253—255° (decomp.) (from water) and mixed m. p. 238° with 5-methoxytrytophan. This may have been a stereoisomer of (IV) but was too small in quantity for further investigation.

7-*Methoxy-2-methyl-β-carboline* (*7-methoxyharman*) (III) was prepared from the above acid by the procedure described for analogous cases (Jacobs and Craig, *J. Biol. Chem.*, 1936, **113**, 759; cf. Harvey and Robson, *J.*, 1938, 97). The acid (0·5 g.), dissolved in boiling water (120 c.c.), was oxidised with 10% aqueous potassium dichromate (25 c.c.) followed by acetic acid (5 c.c.). The whole was boiled for 3 minutes and the cooled mixture, in which a yellow solid had separated, was treated with an excess of aqueous sodium sulphite and then with a saturated solution of sodium carbonate. After 2 hours at 0° the solid was collected (and was slightly augmented by material recovered from an ethereal extract of the filtrate—total yield, 0·255 g.) and afforded 7-methoxyharman as pale straw-coloured prisms, m. p. 275—276°, from methanol (Späth and Lederer, *loc. cit.*, give m. p. 273°) (Found: C, 73·7; H, 5·8; N, 12·9. Calc. for $C_{13}H_{12}ON_2$: C, 73·6; H, 5·7; N, 13·2%). 7-Methoxyharman gives a yellow solution in dilute hydrochloric acid; addition of ethanol produces a pale yellow-green fluorescence.

7-*Methoxy-2* : 3-*dimethyl-β-carbolinium Methosulphate and Hydroxide* (VI; X = $MeSO_4$ and OH).—When a suspension of the base (III) (0·25 g.) in benzene (6 c.c.) and methyl sulphate (0·25 c.c.) was heated under reflux for 1 hour the mixture became pasty and light yellow in colour. After 12 hours at room temperature, removal of the solvent afforded the crude *methosulphate* which crystallised in slender yellow needles, m. p. 210—211° (from methanol), containing a molecule of solvent (Found, after drying at 100°/15 mm. for 3 hours: C, 52·0; H, 5·8. $C_{14}H_{16}ON_2.MeSO_4.MeOH$ requires C, 51·9; H, 5·9%). By repeated crystallisation or by warming with dilute sulphuric acid the methosulphate was changed to a *salt*, possibly the hydrogen sulphate, which had a strongly acid reaction and formed greenish-yellow rods of m. p. 276—278° (uncorr.) from methanol, again retaining a molecule of solvent (Found: C, 50·8; H, 5·3. $C_{14}H_{16}ON_2.HSO_4.MeOH$ requires C, 50·6; H, 5·6%). Addition of dilute aqueous sodium hydroxide to a solution of the methosulphate (0·15 g. of m. p. 210°) in water (3 c.c.) caused

precipitation of the *hydroxide* which formed tufts of yellow needles (from water), losing water at *ca.* 100°, softening above 210° and gradually melting to a dark brown liquid at *ca.* 225° [Found, (i) after drying at 20°/18 mm. for 2 days: C, 68·5; H, 6·5; N, 11·2; (ii) after drying at 100—110°/18 mm. for 7 hours: C, 74·0; H, 5·85. $C_{14}H_{14}ON_2.H_2O$ requires C, 68·85; H, 6·6; N, 11·5. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2%].

7-*Methoxy*-1 : 2 : 3-*trimethyl*-β-*carbolinium Iodide* (VIII).—The foregoing hydroxide (0·2 g.), after being heated at 100°/15 mm. for 30 minutes, cooled, and suspended in dry benzene (2 c.c.), was treated with methyl iodide (1 c.c.) and the mixture was warmed under reflux at 45—50° for 3 hours. After 12 hours at room temperature the solvent was removed, affording the *methiodide* which formed slender yellow needles, m. p. *ca.* 320° (decomp.), from water (Found: C, 49·0; H, 4·7; N, 7·4. $C_{14}H_{14}ON_2.CH_3I$ requires C, 48·9; H, 4·6; N, 7·6%).

7-*Methoxy*-1 : 2-*dimethyl*-β-*carboline* (II).—The above methiodide (50 mg.) was heated in a sublimation tube at 300—310°/15 mm., affording a yellowish sublimate (30 mg.) which, after renewed sublimation at 135—140°/15 mm., gave the *carboline* (II) as almost colourless lustrous plates of m. p. 80—81°, resolidifying and re-melting at 130—131° (from ethanol–water) (Found, after drying at 100°/15 mm. for 3 hours: C, 74·2; H, 6·1; N, 12·4. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2; N, 12·4%). The compound (II) was readily soluble in dilute acid giving a yellow solution which fluoresced pale green-yellow on addition of ethanol. The *picrate* formed yellow needles, m. p. 277—278° (decomp.) with softening at 260°, from ethanol (Found: C, 52·7; H, 3·45. $C_{14}H_{14}ON_2.C_6H_3O_7N_3$ requires C, 52·75; H, 3·7%). For conversion into the *p*-nitrobenzylidene derivative, the base (II) (10 mg.) was heated with *p*-nitrobenzaldehyde (50 mg.) for 5 minutes at 250—255°. The cooled mixture was then treated with benzene and dilute hydrochloric acid, affording an insoluble hydrochloride which was filtered off, washed with benzene, and decomposed by rubbing it with cold dilute sodium hydroxide. The resulting powder was washed with water and extracted with hot benzene from which, on cooling, the p-*nitrobenzylidene* derivative separated as brick-red needles, m. p. 230—231° after further crystallisation (Found: C, 69·8; H, 4·5. $C_{21}H_{17}O_3N_3$ requires C, 70·2; H, 4·7%).

as-*p*-Methoxyphenylmethylhydrazine, b. p. (uncorr.) 134—138°/10 mm., was prepared by reduction of *N*-nitroso-*N*-methyl-*p*-anisidine, using zinc and acetic acid essentially as described by Späth and Brunner (*Ber.*, 1925, **58**, 522) but the following points were noted: (*a*) the use of partially oxidised (" aged ") zinc dust is preferable to that of fresh zinc powder since the latter reagent produces a greater proportion of *N*-methyl-*p*-anisidine: (*b*) aluminium amalgam in moist ether gives good results: (*c*) prolonged boiling during vacuum-distillation is to be avoided since decomposition to *N*-methyl-*p*-anisidine occurs (cf. Chattaway and Aldridge, *J.*, 1911, **99**, 404). For characterisation *as*-*p*-methoxyphenylmethylhydrazine was converted into its *benzylidene* derivative, pale yellow plates of m. p. 130—131° (from ethanol), which is formed when a solution of the hydrazine in acetic acid is mixed with one of benzaldehyde in ethanol (Found: N, 11·3. $C_{15}H_{16}ON_2$ requires N, 11·7%).

5-*Methoxy*-1-*methylindole*-2-*carboxylic Acid.*—*as*-*p*-Methoxyphenylmethylhydrazine (50 g.) was treated under cooling with a solution of pyruvic acid (29 g.) in water (15 c.c.). After 12 hours the supernatant liquid was decanted from the oily hydrazone, the latter was dissolved in a solution of concentrated sulphuric acid (25 g.) in ethanol–water (1 : 1, 150 c.c.), and the whole was warmed until reaction occurred whereby the temperature rose to 75°. The product (14 g.) separated on cooling and storage and formed pale yellow leaflets, m. p. 219—220° (decomp.), from ethanol (Found: C, 64·15; H, 5·3; N, 6·7. Calc. for $C_{11}H_{11}O_3N$: C, 64·4; H, 5·4; N, 6·8%): Kermack and Tebrich (*J.*, 1940, 314) give m. p. 216°.

5-*Methoxy*-1-*methylindole* (IX).—(*a*) 5-Methoxy-1-methylindole-2-carboxylic acid (10 g.) was heated in a Claisen flask at 760 mm. and 220—225° (bath-temp.). When frothing had subsided the pressure was gradually reduced to 20 mm. and the *product* distilled (7·3 g.). After purification by sublimation, it formed white lustrous plates, m. p. 103—104°, from ethanol (Found: C, 74·6; H, 6·7; N, 9·1. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8; N, 8·7%) and afforded a *picrate* as dark red needles of m. p. 111—112° from ethanol (Found: C, 49·5; H, 3·6; N, 14·5. $C_{16}H_{14}ON_4C_6H_3O_7N_3$ requires C, 49·2; H, 3·6; N, 14·4%). (*b*) 5-Methoxy-1-methyloxindole (1 g.) of m. p. 96—97° (cf. Porter, Robinson, and Wyler, *J.*, 1941, 620, who give m. p. 92°) was dissolved in ether (10 c.c.) and treated with a solution of lithium aluminium hydride (0·15 g.) in ether (6 c.c.), which was added with stirring during 10 minutes. Stirring was continued for a further 10 minutes, then water (2·5 c.c.) followed by 4% hydrochloric acid (2·5 c.c.) was cautiously added. After renewed washing the ether solution was separated and evaporated. The residue was distilled in steam and the distillate was extracted with ether from which the indole (0·36 g.), m. p. 103—104° [from light petroleum (b. p. 60—80°)], was recovered and was identified with the product from (*a*) by mixed m. p. and formation of the picrate.

The acid washings from (*b*) on basification and recovery from ether afforded a small quantity of oil which when treated with a solution of picric acid in ethanol yielded the *picrate* of 5-methoxy-1-methylindoline as yellow prisms, softening at 165° and melting at 171—173° (decomp.) (from methanol) (Found: C, 49·2; H, 4·2; N, 14·1. $C_{10}H_{13}ON,C_6H_3O_7N_3$ requires C, 49·0; H, 4·1; N, 14·3%).

3-*Dimethylaminomethyl*-5-*methoxy*-1-*methylindole* (5-*methoxy*-1-*methylgramine*) was prepared from 5-methoxy-1-methylindole by the method described above for 5-methoxygramine (cf. Snyder and Eliel, *J. Amer. Chem. Soc.*, 1948, **70**, 1703). When precipitated, by means of 10% aqueous sodium hydroxide from its solution in ice-cold N-hydrochloric acid, it formed an almost colourless crystalline powder which, in a vaccum-desiccator, first liquefied, then re-solidified and thereafter crystallised as colourless prisms, m. p. 43—45°, from light petroleum (b. p. 60—80°) (Found: C, 71·3; H, 8·2; N, 12·95. $C_{12}H_{16}ON_2$ requires C, 71·6; H, 8·3; N, 12·8%). The base appeared to form both a dipicrate and a *monopicrate*. The former, which was rather unstable, separated as dark-red rectangular slabs of purple lustre and m. p. 129—130° when the base was treated with a concentrated solution of picric acid in benzene–ethanol (Found: C, 45·3; H, 3·5; N, 15·8 and 16·15. Calc. for $C_{12}H_{16}ON_2.2C_6H_3O_7N_3$: C, 44·4; H, 3·55; N, 16·6%) and, on attempted recrystallisation from benzene–ethanol, dissociated into the well-defined

monopicrate, orange needles of m. p. 143—144° (decomp.) (Found: C, 51·3; H, 4·9; N, 15·9. $C_{13}H_{18}ON_2.C_6H_3O_7N_3$ requires C, 51·0; H, 4·7; N, 15·7%). The *methiodide* of the base was formed when its components were mixed in ethanol at 0°, and was collected after 10 hours. It crystallised from ethanol as colourless prisms which sintered at *ca.* 180° and decomposed gradually above 200° (Found: C, 47·0; H, 5·7; N, 7·9. $C_{14}H_{21}ON_2I$ requires C, 46·7; H, 5·8; N, 7·8%).

Ethyl α-Acetamido-α-carbethoxy-β-(5-methoxy-1-methyl-3-indolyl)propionate.—The method which was successful in the analogous preparation (cf. above) from 5-methoxygramine miscarried when applied to 5-methoxy-1-methylgramine but the following procedure based on that of Snyder and Smith (*J. Amer. Chem. Soc.*, 1944, **66**, 350; cf. Snyder and Eliel, *ibid.*, 1949, **71**, 663) proved to be effective: 5-Methoxy-1-methylgramine methiodide (3·0 g.) was added to a solution of ethyl acetamidomalonate (1·8 g.) in ethanol (17 c.c.) containing sodium ethoxide (from 0·19 g. of sodium), and the whole was heated under reflux for 32 hours by which time evolution of trimethylamine had practically ceased. After filtration and partial concentration the solution was added to cold water (120 c.c.), the precipitated gum readily becoming solid (2·8 g.). It was purified for analysis by passage of a solution in benzene through a column of alumina, the recovered *ester* being obtained as colourless prisms, m. p. 122—123°, from benzene–light petroleum (b. p. 60—80°) and then from ethanol–water (Found: C, 61·5; H, 7·0; N, 7·6. $C_{20}H_{24}O_6N_2$ requires C, 61·5; H, 6·7; N, 7·2%).

α-Acetamido-β-(5-methoxy-1-methyl-3-indolyl)propionic Acid.—According to the general procedure of Albertson (*J. Amer. Chem. Soc.*, 1950, **72**, 1396) the above crude ester (2·5 c.c.) was heated under reflux with a solution of sodium carbonate (2·5 g.) in water (25 c.c.) for 17 hours, after which only a small quantity of a dark oil remained undissolved. The mixture was extracted with ether, and the separated aqueous layer was acidified and set aside at 0°. The solid acid (1·7 g.) was collected and crystallised as leaflets, m. p. 211—212°, from ethanol–water (1 : 2) (Found: C, 62·3; H, 6·2; N, 9·5. $C_{14}H_{16}O_4N_2$ requires C, 62·1; H, 6·2; N, 9·65%).

α-Amino-β-(5-methoxy-1-methyl-3-indolyl)propionic Acid (*5-Methoxy-1-methyltryptophan*).—The above acetyl derivative (1·1 g.) was heated (6 hours) with water (15 c.c.) in a sealed tube at 200° (for procedure cf. Rinderknecht and Niemann, *J. Amer. Chem. Soc.*, 1948, **71**, 2296). The solid obtained by filtration and some recovery from the concentrated mother-liquor (total, 0·84 g.) gave *5-methoxy-1-methyltryptophan* as colourless needles, m. p. 264—265° (decomp.), from ethanol–water (1 : 2) (Found: C, 62·7; H, 6·5; N, 11·5. $C_{13}H_{16}O_3N_2$ requires C, 62·9; H, 6·45; N, 11·3%).

2 : 3 : 4 : 5-*Tetrahydro-7-methoxy*-1 : 2-*dimethyl-β-carboline-4-carboxylic acid* was prepared, as described for (IV), from 5-methoxy-1-methyltryptophan (0·5 g.), the product, however, separating only after the reaction solution had been concentrated from 50 c.c. to 10 c.c. under reduced pressure. The crude acid (0·5 g.) was separated by fractional crystallisation from ethanol into (i) a main fraction consisting of colourless needles, m. p. 268—269° (decomp.) (Found: C, 64·9; H, 6·25. $C_{15}H_{16}O_3N_2$ requires C, 65·7; H, 6·6%), and (ii) a second smaller fraction of pointed leaflets, m. p. 244—245° (decomp.) (Found: C, 64·95; H, 6·2%). These two fractions appeared to be distinct and the compounds are possibly stereoisomers although mixed m. p. determinations gave inconclusive results; moreover, admixture of the second fraction with the distinct acid (IV) again produced no depression of m. p. The difficulty in obtaining satisfactory analytical figures for this type of compound has been experienced previously (cf. Snyder *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 219).

Conversion into 7-*methoxy*-1 : 2-*dimethyl-β-carboline* (II). The above acid yielded (II) when oxidised as described in the preparation of (III) from (IV). The product, recovered in ether from the reaction mixture and purified on alumina with benzene–light petroleum (1 : 1) as solvent, crystallised as colourless, glistening needles, m. p. 130—131°, from ethanol–water (1 : 1) or as plates, m. p. 80—81°, re-solidifying and re-melting at 130—131°, from a more aqueous solvent. This melting behaviour was unaffected by admixture with the previous specimen of 7-methoxy-1 : 2-dimethyl-β-carboline. Both samples gave the same picrate and *p*-nitrobenzylidene derivative.

A hydrochloride, yellow needles of m. p. 286—287° (decomp.), and a nitrate, yellow needles of m. p. 210—211° (sharp decomp.), were prepared but were not analysed.

The following table shows the results of m. p. and mixed m. p. determinations on the degradation products (A) from mitragynine and their isomers (B) of the 7-methoxy-1 : 2-dimethyl-β-carboline type:

	A.	B.	A + B.
Base	softens 120°; m. p. 129—134°	m. p.s 80—81° and 130—131°	m. p. 92—102°
Picrate	decomp. 260—262°	decomp. 277—278°	decomp. 256°
p-Nitrobenzylidene derivative	m. p. 260—261°	m. p. 230—231°	m. p. 227—228°

This investigation was initiated following preliminary experiments by Dr. G. M. Badger and Dr. P. G. Raison, to whom we are indebted for very helpful discussion and suggestions. We also thank the University of Glasgow for a Research Award (to P. McC.). Microanalyses were carried out by Miss R. H. Kennaway.

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270. *The Nuclear Chlorination of Toluene: 2 : 3 : 4- and 2 : 3 : 6-Trichlorotoluene.*

By H. C. Brimelow, R. L. Jones, and T. P. Metcalfe.

Nuclear chlorination of toluene or *o*-chlorotoluene to the trichloro-stage in the presence of an iron catalyst is shown to yield 2 : 4 : 5- and 2 : 3 : 6-trichlorotoluene together with small amounts of 2 : 3 : 4-trichlorotoluene and not, as previously recorded, 2 : 4 : 5- and 2 : 3 : 4-trichlorotoluene only. The m. p. of 2 : 3 : 6-trichlorobenzoic acid is 124—126° and not 163—164° as hitherto recorded.

In connection with another research, it was necessary to prepare authentic samples of all the possible chlorinated derivatives of benzaldehyde and benzoic acid. These preparations, with two exceptions, were carried out without difficulty by methods described in the literature. The exceptions were the 2 : 3 : 4- and 2 : 3 : 6-trichloro-derivatives, and it became clear that the literature on these compounds was seriously in error. According to Seelig (*Annalen*, 1887, **237**, 129) and Prenntzell (*ibid.*, 1897, **296**, 181) chlorination of toluene or *o*- or *p*-chlorotoluene in the presence of an iron catalyst to the trichloro-stage gives mainly a mixture of 2 : 3 : 4- and 2 : 4 : 5-trichlorotoluene. We have now found that the major products obtained from toluene and *o*-chlorotoluene are 2 : 3 : 6- and 2 : 4 : 5-trichlorotoluene, the 2 : 3 : 4-isomer occurring only to a limited extent. We have found that the trichlorobenzoic acids are the most satisfactory derivatives for characterising the trichlorotoluenes.

The constitution of 2 : 4 : 5-trichlorotoluene was not in doubt and it was readily separated from the mixture by sulphonation and fractional desulphonation (Prenntzell, *loc. cit.*). The problem, therefore, was the identification of the 2 : 3 : 4- and 2 : 3 : 6-trichlorotoluene. For this purpose authentic samples of the corresponding benzoic acids were required. 2 : 3 : 6-Trichlorobenzoic acid, m. p. 124—126°, was prepared (*a*) from 3 : 6-dichloroanthranilic acid by the Sandmeyer reaction, (*b*) by direct oxidation of 2 : 3 : 6-trichlorotoluene with nitric acid, and (*c*) by oxidation of 2 : 3 : 6-trichlorobenzaldehyde with potassium permanganate or nitric acid. 2 : 3 : 6-Trichlorotoluene was prepared in two ways: from 3-amino-2 : 6-dichlorotoluene by the Sandmeyer reaction (Cohen and Dakin, *J.*, 1902, **81**, 1331), and by chlorination of toluene-*p*-sulphonyl chloride followed by hydrolysis of the resulting 2 : 3 : 6-trichlorotoluene-4-sulphonyl chloride (D.R.-P. 210856; "Friedländer," **9**, 104). 2 : 3 : 6-Trichlorobenzaldehyde was obtained by exhaustive chlorination of the trichlorotoluene side-chain to the benzylidene chloride, followed by hydrolysis of the latter. This method has the advantage that traces of isomeric trichlorotoluenes, other than those substituted in the 2- and the 6-position, are converted into the corresponding benzotrichlorides and benzoic acids and readily separated from the 2 : 3 : 6-trichlorobenzaldehyde.

The 2 : 3 : 6-trichlorobenzaldehyde so prepared had m. p. 87—88°, in agreement with D.R.-P. 199,943 ("Friedländer," **9**, 204); it was then obtained from 3-amino-2 : 6-dichlorobenzaldehyde by replacement of the amino-group with chlorine. The remote possibility that we were dealing with the 2 : 3 : 4-isomers was disproved by the unambiguous synthesis of and comparison with 2 : 3 : 4-trichloro-benzaldehyde and -benzoic acid. Cohen and Dakin (*loc. cit.*) record the m. p. of 2 : 3 : 6-trichlorobenzoic acid as 163—164°; this is clearly an error.

2 : 3 : 4-Trichlorobenzoic acid, m. p. 187—188°, was prepared (*a*) by direct oxidation of 2 : 3 : 4-trichlorotoluene and (*b*) by oxidation of 2 : 3 : 4-trichlorobenzaldehyde with aqueous permanganate. 2 : 3 : 4-Trichlorotoluene was prepared by chlorination of *p*-chlorotoluene (followed by separation of the large amount of the 2 : 4 : 5-isomer) (Seelig, *loc. cit.*) and also by chlorination of 3-aminotoluene-6-sulphonamide with hydrogen peroxide and hydrochloric acid. The resulting 3-amino-2 : 4-dichlorotoluene-6-sulphonamide, on removal of the sulphonamido-group, yielded 3-amino-2 : 4-dichlorotoluene which gave 2 : 3 : 4-trichlorotoluene on replacement of the amino-group with chlorine. 2 : 3 : 4-Trichlorobenzaldehyde, m. p. 86°, was obtained by regulated side-chain chlorination of the toluene, followed by hydrolysis.

Cohen and Dakin (*J.*, 1902, **81**, 1327, 1347) record the synthesis of 2 : 3 : 4-trichlorotoluene from 2 : 3-dichlorotoluene by nitration, reduction, and replacement of the amino-group with chlorine. On oxidation of their product they obtained a trichlorobenzoic acid of m. p. 186—187°, which we confirm as the m. p. of the 2 : 3 : 4-isomer. Repetition of this synthesis, how-

ever, incorporating a vigorous purification of the dichlorotoluidine by repeated recrystallisation of its acetyl derivative, has given 2 : 3 : 6-trichlorotoluene in low yield, identified by conversion into 2 : 3 : 6-trichlorobenzaldehyde (m. p. and mixed m. p.). It thus appears that Cohen and Dakin obtained a mixture of 2 : 3-dichloro-4-nitro- and 2 : 3-dichloro-6-nitro-toluene and that their product was a mixture of 2 : 3 : 4- and 2 : 3 : 6-trichlorotoluene. We have found repeatedly that when such a mixture is chlorinated to exhaustion in the side-chain, and the products are hydrolysed, a readily separable mixture of 2 : 3 : 6-trichlorobenzaldehyde and 2 : 3 : 4-trichlorobenzoic acid results, while if the mixture is oxidised with dilute nitric acid 2 : 3 : 4-trichlorobenzoic acid results, because this acid is less soluble in water than the 2 : 3 : 6-isomer, and because 2 : 3 : 6-trichlorotoluene is less readily oxidised by dilute nitric acid.

In addition to the method mentioned above, 2 : 3 : 4-trichlorobenzaldehyde, m. p. 86°, was also obtained by side-chain chlorination of the mixture of 2 : 3 : 6- and 2 : 3 : 4-trichlorotoluene (mentioned above) by using a deficiency of chlorine, followed by hydrolysis. Its m. p. is almost coincident with that of 2 : 3 : 6-trichlorobenzaldehyde but the m. p. of a mixture of the two shows a marked depression.

Seelig (*loc. cit.*) and Cohen and Dakin (*loc. cit.*) made use of the mono- and di-nitro-derivatives for characterisation of 2 : 3 : 4- and 2 : 3 : 6-trichlorotoluene. In view of the above findings we examined these compounds. The necessary pure trichlorotoluenes were made as follows: 2 : 3 : 4-trichlorotoluene from *p*-chlorotoluene and from 3-aminotoluene-6-sulphonamide as above; 2 : 3 : 6-trichlorotoluene by a very easy Wolff–Kishner reduction of purified 2 : 3 : 6-trichlorobenzaldehyde. The mono- and di-nitro-derivatives were made by recorded methods (Cohen and Dakin, *J.*, 1902, **81**, 1327). Their m. p.s are recorded, together with those of other derivatives of 2 : 3 : 4- and 2 : 3 : 6-trichlorotoluene, in the table below.

The m. p. of 2 : 3 : 4-trichloronitrotoluene was found to be 70°; *i.e.*, 10° higher than that recorded for this substance by Cohen and Dakin (*loc. cit.*, p. 1328). The m. p.s of 2 : 3 : 4- and 2 : 3 : 6-trichlorodinitrotoluene are identical, but mixtures of the two in varying proportions show a small but definite depression of m. p.

Derivative of:	2 : 3 : 4-Trichloro-, m. p.	2 : 3 : 6-Trichloro-, m. p.
Toluene	43—44°	43—44°
Nitrotoluene	70	59—60
Dinitrotoluene	143	143
Benzylidene chloride	—	78—80
Benzaldehyde	86	87—88
Benzoic acid	187—188	124—126

2 : 3 : 6-Trichloro-benzaldoxime, -benzylamine, and -benzyl alcohol have also been prepared.

Experimental.

(M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.)

2 : 3 : 6-*Trichlorotoluene*.—(1) 3-Amino-2 : 6-dichlorotoluene (37·2 g.; m. p. 52°) was diazotised at 0—5° in hydrochloric acid (*d* 1·18; 93 c.c.) and water (93 c.c.) by the slow addition of powdered sodium nitrite (14·8 g.). The cold filtered solution of the diazonium salt was added, during 15 minutes, to a solution of cuprous chloride (46·5 g.) in 15% hydrochloric acid (370 c.c.) at 25°. The temperature rose to 40° during the addition. After 15 minutes, the trichlorotoluene was distilled in steam from the reaction mixture, separated, and dried at room temperature, giving waxy cubes (31·0 g.), m. p. 39—40°. On chlorination of the side-chain at 180—200°, a solid benzylidene chloride (needles, m. p. 78—80°, from ethanol) was obtained which gave 2 : 3 : 6-trichlorobenzaldehyde, m. p. 87—88°, on hydrolysis.

(2) Crude toluene-*p*-sulphonyl chloride (1000 g.) was washed with water (1500 c.c.) at 75°, and the oil separated, dried ($CaCl_2$), and screened through a 200-mesh gauze yielding the purified material (850 g.). This was heated to 70—80°, antimony trichloride (25 g.) added, and chlorine passed into the stirred mixture until a gain in weight of 460 g. was obtained (7½ hours). The product (1335 g.) was added during 1 hour to 86% sulphuric acid (200 g.) kept at 230—240° in a steam-distillation apparatus supplied with steam superheated to 240—250°. Crude 2 : 3 : 6-trichlorotoluene collected in the receiver. It was washed with water at 70° and redistilled in superheated steam. The crude material was further washed with water until it was neutral to litmus (yield, 600 g.). It was purified by distillation *in vacuo* through a column equivalent to 50 theoretical plates; the distillate (385 g.; b. p. 118°/18 mm.) crystallised in waxy needles, m. p. 40—42°, from ethanol or methanol. On oxidation with 60% nitric acid at 150° it yielded 2 : 3 : 6-trichlorobenzoic acid, m. p. 124—126°, and on chlorination of the side-chain behaved in the same way as the sample prepared from 3-amino-2 : 6-dichlorotoluene.

(3) Dry toluene (or *o*-chlorotoluene) was chlorinated to the trichloro-stage in the presence of ¼—1% of iron filings. The temperature was allowed to rise from 10° to 15° during the introduction of the first chlorine atom, then held at 20° until near completion, and the final 5% of chlorine introduced at 20—40°. The crude chlorinated toluenes (981 g.) were added with stirring to 23% oleum (1930 g.). The

temperature rose to 70—80° and was kept thereat for a further 45 minutes. 33% Sulphuric acid (1800 g.) was added cautiously, the temperature being allowed to rise to 130—140°. The mixture was then distilled in superheated steam. The temperature was gradually raised as the distillation proceeded. From 160° to 200°, crude 2 : 4 : 5-trichlorotoluene collected in the receiver (463 g. *ex* toluene, or 330 g. *ex o*-chlorotoluene). Between 200° and 210° small amounts (80—90 g.) of liquid chlorotoluenes were collected, and between 210° and 230° impure 2 : 3 : 6-trichlorotoluene (405 g. *ex* toluene; 543 g. *ex o*-chlorotoluene) containing *ca.* 2—3% of 2 : 3 : 4-trichlorotoluene and higher chlorinated toluenes. The last fraction was washed with warm water and fractionally distilled *in vacuo* through a column equivalent to 50 theoretical plates. 2 : 3 : 6-Trichlorotoluene was obtained, of b. p. 118°/18 mm., m. p. 39—40°, containing 3—4% of the 2 : 3 : 4-isomer. It constituted 62% of the material fractionated in the case of toluene and 81% in the case of *o*-chlorotoluene. If the temperature in the initial stages of chlorination was allowed to rise to 30—40° the 2 : 3 : 6-trichlorotoluene fraction was smaller and the proportion of 2 : 4 : 5-trichlorotoluene increased.

(4) 2 : 3 : 6-Trichlorobenzaldehyde, m. p. 78° (21 g.), was added to a solution of hydrazine hydrate (50%; 20 c.c.) in ethylene glycol (200 c.c.). The solution was warmed to 90° and set aside for 1 hour. The temperature was then raised to 80°, and powdered sodium hydroxide (12 g.) added. The temperature rose to 100° with a brisk evolution of nitrogen. The mixture was heated to 110° for 10 minutes, allowed to cool somewhat, and poured into water (500 c.c.), and the whole distilled in steam. 2 : 3 : 6-Trichlorotoluene (15·2 g.) collected in the receiver and was filtered off and dried at room temperature; it formed waxy cubes melting sharply at 43—44°. Recrystallisation from ethanol or methanol gave waxy white needles of unchanged m. p. This material was used to prepare mono- and di-nitro-derivatives.

(5) 2 : 3-Dichloronitrotoluene was prepared by Cohen and Dakin's method (*J.*, 1902, **81**, 1347). 2 : 3-Dichlorotoluene (70 g.; f. p. 6°) was added to nitric acid (*d* 1·5; 84 c.c.) at 10—20° with stirring; the mixture was kept for 1 hour, then poured into water (400 c.c.), and the precipitate was filtered off; the product (88 g.; m. p. 49—52°) was a waxy solid; its m. p. was unaffected by recrystallisation from ethanol. 2 : 3-Dichloronitrotoluene (85 g.) was added during 1½ hours to a well-stirred solution of stannous chloride (290 g.) in hydrochloric acid (*d* 1·16; 290 c.c.) at 70—80°. The temperature was then raised to 95° and kept thereat for 20 minutes. The clear solution was poured into water, made alkaline with aqueous sodium hydroxide, and distilled in steam. Crude amino-2 : 3-dichlorotoluene, m. p. 40° (63 g.), was collected. This base (60 g.) was acetylated by stirring it for 1 hour at 45° with water (300 c.c.) and acetic anhydride (42 g.). The solid was collected and twice crystallised from ethanol–water. This material (27 g.), m. p. 131—133°, was boiled with 65% sulphuric acid (150 c.c.) for 2 hours. The clear solution was cooled, poured into water, basified with aqueous sodium hydroxide, and distilled in steam. Crude amino-2 : 3-dichlorotoluene (20 g.), m. p. 35° (not sharp), was collected. It was diazotised at 0° with hydrochloric acid (*d* 1·16; 48 c.c.), water (500 c.c.), and sodium nitrite (8·0 g.). The clear solution of the diazonium chloride was added at 0° to a solution of cuprous chloride (25 g.) in hydrochloric acid (*d* 1·16; 95 c.c.) and water (95 c.c.). The mixture was kept for 1 hour, and the trichlorotoluene (6·2 g.) distilled from it in steam. The product was a waxy solid, m. p. 35°, which could not be purified by crystallisation from methanol or ethanol, but was shown to consist largely of 2 : 3 : 6-trichlorotoluene by chlorination of the side-chain at 180—200° followed by hydrolysis of the solid benzylidene chloride formed, giving 2 : 3 : 6-trichlorobenzaldehyde (isolated in good yield *via* the bisulphite compound), m. p. 87—88°, identical (mixed m. p.) with material obtained from authentic 2 : 3 : 6-trichlorotoluene. The crude aldehyde contained only traces of alkali-soluble material.

2 : 3 : 6-*Trichlorobenzaldehyde.*—2 : 3 : 6-Trichlorotoluene (20 g.), prepared by any of the above methods, was chlorinated at 180—220° until no further absorption of chlorine occurred, an uptake corresponding to 2 atoms of chlorine being obtained in 24 hours. On cooling, the reaction mixture solidified. (A small portion of this material on crystallisation from ethanol had m. p. 78—80°.) It was added gradually with good stirring to 98% sulphuric acid (100 g.) at 75°. When evolution of hydrogen chloride slackened (1 hour) the temperature was raised to 95° and kept thereat for 30 minutes. After cooling to room temperature, the mixture was poured on ice and water, and the light cream-coloured solid filtered off and purified by distillation in steam; the product (20·2 g.; m. p. 84—85°) recrystallised from ethanol–water or light petroleum (b. p. 80—100°) in needles, m. p. 87—88°. If the 2 : 3 : 6-trichlorotoluene used contained any of the 2 : 3 : 4-isomer, the yield was somewhat lower and the chlorine uptake slightly greater, since 2 : 3 : 4-trichlorotoluene is readily chlorinated to the benzotrichloride stage. The 2 : 3 : 4-trichlorobenzoic acid, m. p. 187—188°, was isolated by extraction of the crude aldehyde with dilute aqueous sodium carbonate.

2 : 3 : 6-*Trichlorobenzoic Acid.*—(1) 2 : 3 : 6-Trichlorobenzaldehyde (2·1 g.) was stirred with a 1% aqueous solution of potassium permanganate (105 c.c.) at 90—95°. When the permanganate was decolorised, the hot suspension was filtered, the filtrate acidified with hydrochloric acid, and 2 : 3 : 6-trichlorobenzoic acid precipitated by addition of sodium chloride. It was collected and recrystallised from water; it (0·54 g.) had m. p. 124—126°. This acid is more soluble in water than the 2 : 3 : 4-isomer and corresponds with the description given by Seelig (*loc. cit.*) for " 2 : 3 : 4"-trichlorobenzoic acid.

(2) 2 : 3 : 6-Trichlorobenzaldehyde (50 g.) was stirred vigorously at 95° with 30% nitric acid (1450 g.) until a test portion showed almost complete solubility in dilute aqueous sodium hydroxide (5 hours). The reaction mixture was then cooled and basified with sodium hydroxide, and the faintly turbid solution clarified by extraction with benzene, treated with carbon, filtered, and slowly acidified with dilute hydrochloric acid with stirring. The precipitated 2 : 3 : 6-trichlorobenzoic acid was collected, washed with water, and dried at room temperature, giving a product (50 g.) of m. p. 124—126°.

(3) 3 : 6-Dichloroanthranilic acid (8·0 g.), m. p. 153° (Villiger, *Ber.*, 1909, **42**, 3539), was dissolved in an aqueous solution (120 c.c.) of an equivalent of sodium carbonate, and sodium nitrite (2·8 g.) added. This solution was added at 0—5° to 12% hydrochloric acid (85 c.c.). The resulting solution of the

diazonium chloride was added to a solution of cuprous chloride (4·0 g.) in 15% hydrochloric acid (100 c.c.) at −25°. The mixture was allowed to warm to room temperature, and then heated momentarily to the b. p. The suspension was cooled, the solid was filtered off and extracted with dilute sodium carbonate solution, and the filtered extracts were acidified. The crude 2 : 3 : 6-*trichlorobenzoic acid* was recrystallised from water (yield 0·4 g.), m. p. 124—126° (Found: C, 37·5; H, 1·6; Cl, 47·0. $C_7H_3O_2Cl_3$ requires C, 37·25; H, 1·3; Cl, 47·2%).

(4) 2 : 3 : 6-Trichlorotoluene (2·6 g.) was heated for 6 hours at 150° with 60% nitric acid (40 c.c.) in a sealed tube. The resulting mixture was diluted with water and evaporated to dryness on the steam-bath. The crude 2 : 3 : 6-trichlorobenzoic acid was extracted with aqueous sodium hydrogen carbonate, and the solution treated with carbon, filtered, and acidified (yield, 1·3 g.; m. p. 124° raised to 124—126° on recrystallisation from water). This acid was identical (mixed m. p.s) with that obtained by methods (1), (2), and (3), above (Found: C, 36·95; H, 1·45; Cl, 46·7%).

2 : 3 : 4-*Trichlorotoluene*.—(1) *p*-Chlorotoluene was chlorinated in the presence of 1% of iron filings below 30°. Slightly more than the theoretical gain in weight for the production of trichlorotoluene was obtained. The product was washed with water until neutral, separated, and dried. The crude trichlorotoluene (370 g.) was sulphonated and fractionally desulphonated as previously described for the preparation of 2 : 3 : 6-trichlorotoluene from toluene or *o*-chlorotoluene. The distillation in superheated steam from sulphuric acid yielded: at 160—180°, impure 2 : 4 : 5-trichlorotoluene (236 g.); at 190—210°, a liquid of unknown composition (64 g.); and at 210—230°, a white crystalline solid (42 g.). The last fraction, on distillation, all boiled at 244°/760 mm. The distilled material was recrystallised from ethanol giving 2 : 3 : 4-trichlorotoluene in white needles (25 g.), m. p. 43—44°.

(2) 3-Aminotoluene-6-sulphonamide, m. p. 168° (Backeberg and Marais, *J.*, 1943, 78) (26·6 g.), was dissolved in a mixture of hydrochloric acid (*d* 1·16; 300 c.c.) and water (450 c.c.) at 60°. At this temperature a solution of hydrogen peroxide (100-vol.; 30 c.c.) in water (30 c.c.) was added in four equal portions during 30 minutes with good stirring. The mixture was stirred for a further 30 minutes at 60° and then cooled to 25°. The precipitated solid was filtered off and washed with a solution of hydrochloric acid (*d* 1·16; 25 c.c.) in water (75 c.c.) and then with water. The wet filter cake was recrystallised from the minimum of hot glacial acetic acid, the mixture filtered, and the residue washed cautiously with cold acetic acid and dried at 90°; 3-*amino*-2 : 4-*dichlorotoluene*-6-*sulphonamide* (17 g.), formed faintly pink crystals, m. p. 184—185° (Found: C, 33·3; H, 3·4; Cl, 27·3; N, 11·0. $C_7H_8O_2N_2Cl_2S$ requires C, 32·95; H, 3·1; Cl, 27·8; N, 11·0%). 3-Amino-2 : 4-dichlorotoluene-6-sulphonamide (80 g.) was heated at the boil for 2 hours with 70% sulphuric acid (400 c.c.). The reaction mixture was cooled, poured into water (1700 c.c.), and distilled in steam. 3-Amino-2 : 4-dichlorotoluene solidified in the receiver. The distilland contained some unchanged starting material, which was filtered off from the cooled solution and again heated with 70% sulphuric acid, and the dichloroaminotoluene isolated as above. The 3-*amino*-2 : 4-*dichlorotoluene* (total yield, 50 g.) formed white crystals, m. p. 37—38° not raised by recrystallisation from light petroleum (b. p. 80—100°) (Found: C, 47·5; H, 4·05; Cl, 40·7; N, 8·1. $C_7H_7NCl_2$ requires C, 47·7; H, 4·0; Cl, 40·3; N, 7·95%). Its p-*nitrobenzoyl* derivative, needles from ethanol, had m. p. 246° (Found: C, 52·2; H, 3·3; N, 8·35; Cl, 22·6. $C_{14}H_{10}O_3N_2Cl_2$ requires C, 51·7; H, 3·1; N, 8·6; Cl, 21·8%).

3-Amino-2 : 4-dichlorotoluene (22 g.) was dissolved in a hot mixture of hydrochloric acid (*d* 1·16; 290 c.c.) and water (185 c.c.), and the solution cooled quickly; a finely divided suspension was obtained. To this was added, during 1 hour at 10—15°, sodium nitrite (9·0 g.). The filtered solution of the diazonium chloride was added in a thin stream to a boiling solution of cuprous chloride (26·5 g.) in hydrochloric acid (*d* 1·16; 114 c.c.) and water (114 c.c.) in a steam-distillation apparatus, steam being passed through the mixture simultaneously. 2 : 3 : 4-Trichlorotoluene collected in the receiver. It was separated and dried at room temperature (yield, 19 g.; m. p. 36°). Crystallisation from ethanol yielded white needles (8·3 g.), m. p. 42—43°, and a further recrystallisation raised this m. p. to 43—44°. This material did not depress the m. p. of the 2 : 3 : 4-*trichlorotoluene* obtained from *p*-chlorotoluene when admixed with it (Found: C, 43·1; H, 2·6; Cl, 54·0. $C_7H_5Cl_3$ requires C, 42·95; H, 2·6; Cl, 54·5%).

2 : 3 : 4-*Trichlorobenzaldehyde*.—(1) 2 : 3 : 4-Trichlorotoluene (12·0 g.) was chlorinated at 180—200° until an increase in weight corresponding to the uptake of two chlorine atoms was obtained. The crude liquid benzylidene chloride was hydrolysed with 98% sulphuric acid, and the crude aldehyde isolated in the same way as for the 2 : 3 : 6-isomer. It was dissolved in ether, and the solution shaken with concentrated (40%) sodium hydrogen sulphite solution. The bisulphite compound separated, and was filtered off, washed with ether, and dissolved in water, and the aldehyde was precipitated by addition of excess of sodium carbonate. The aldehyde (3·0 g.), m. p. 83°, was crystallised from ethanol–water; it formed needles, m. p. 86°; mixed m. p. with 2 : 3 : 6-trichlorobenzaldehyde, 60—70°. On oxidation with dilute aqueous potassium permanganate it yielded 2 : 3 : 4-trichlorobenzoic acid, m. p. 187—188°.

(2) The mixture of 2 : 3 : 4- and 2 : 3 : 6-trichlorotoluene obtained by chlorinating toluene or *o*-chlorotoluene was chlorinated at 180—200°, the chlorination being stopped when the gain in weight corresponded to the uptake of one chlorine atom. The reaction mixture was hydrolysed with 98% sulphuric acid at 70—90°, and the whole was poured into water, and the gummy solid filtered off. It was then extracted with ether, and the filtered ethereal solution shaken with 40% sodium hydrogen sulphite solution, yielding the aldehyde *via* the bisulphite compound as above. The yield was low and depended on the composition of the starting material, which in turn depended on the conditions of nuclear chlorination.

2 : 3 : 4-*Trichlorobenzoic Acid*.—(1) 2 : 3 : 4-Trichlorotoluene (2·0 g.) was boiled for 16 hours under reflux with 60% nitric acid (50 c.c.). On cooling, 2 : 3 : 4-trichlorobenzoic acid separated. It was collected and dissolved in dilute sodium carbonate solution, from which unchanged toluene was extracted

with ether. On acidification with hydrochloric acid, 2 : 3 : 4-trichlorobenzoic acid was precipitated; it formed needles, m. p. 187—188° (Found: C, 37·5; H, 1·5. Calc. for $C_7H_3O_2Cl_3$: C, 37·3; H, 1·3%).

(2) The mixture of 2 : 3 : 4- and 2 : 3 : 6-trichlorotoluene (above) was chlorinated at 180—200° until no more chlorine was absorbed. The resulting mixture of 2 : 3 : 6-trichlorobenzylidene chloride and 2 : 3 : 4-trichlorobenzotrichloride was hydrolysed with 98% sulphuric acid at 70—90°, and poured into water, and the crude benzaldehyde–benzoic acid mixture dissolved in ether and filtered. The filtered ethereal solution was shaken with concentrated (40%) sodium hydrogen sulphite solution, and the bisulphite compound of 2 : 3 : 6-trichlorobenzaldehyde separated. It was filtered off, and the ethereal portion of the filtrate extracted with aqueous sodium carbonate to obtain 2 : 3 : 4-trichlorobenzoic acid; recrystallised from water, this had m. p. 187—188°. The yield of acid was low and depended on the composition of the starting material.

2 : 3 : 4- *and* 2 : 3 : 6-*Trichloronitrotoluenes.*—These were made by the same method: the toluene (2·0 g.) was added slowly to nitric acid (*d* 1·5; 4 c.c.) at 0—20°. The mixture was kept for one hour, then poured into water, and the precipitated solid was filtered off and recrystallised from ethanol. 2 : 3 : 4-Trichloromononitrotoluene had m. p. 70° (Found: C, 35·2; H, 2·0; Cl, 44·2; N, 6·0. Calc. for $C_7H_4O_2NCl_3$: C, 34·9; H, 1·7; Cl, 44·3; N, 5·8%). The 2 : 3 : 6-trichloromononitrotoluene had m. p. 59—60°.

2 : 3 : 4- *and* 2 : 3 : 6-*Trichlorodinitrotoluenes.*—The toluene (2·0 g.) was heated in the steam-bath with a mixture of nitric acid (*d* 1·5; 16·0 c.c.) and sulphuric acid (*d* 1·84; 9 c.c.) for 30 minutes. The mixture was cooled and poured into water, and the product recrystallised from ethanol. Both 2 : 3 : 4- and 2 : 3 : 6-trichlorodinitrotoluenes had the same m. p., *viz.*, 143°. Mixtures of the two in varying proportions had m. p. 137—139°. 2 : 3 : 4-*Dichloro*-5 : 6-*dinitrotoluene* was analysed (Found: C, 29·8; H, 1·0; N, 9·75. $C_7H_2O_4N_2Cl_2$ requires C, 29·4; H, 1·05; N, 9·8%).

2 : 3 : 6-*Trichlorobenzaldoxime.*—2 : 3 : 6-Trichlorobenzaldehyde (63 g.) was dissolved in ethanol (600 c.c.), and anhydrous sodium carbonate (21 g.) added with stirring. The mixture was heated to 40°, and hydroxylamine hydrochloride (21 g.) in water (100 c.c.) added. The whole was then heated momentarily to the b. p., water (600 c.c.) added, and the solid filtered off and washed with water. Recrystallisation of the *oxime* (55 g.) from ethanol gave white needles, m. p. 169—170° (Found: C, 37·5; H, 1·7; N, 6·3; Cl, 47·5. $C_7H_4ONCl_3$ requires C, 37·4; H, 1·8; N, 6·2; Cl, 47·4%).

2 : 3 : 6-*Trichlorobenzylamine.*—2 : 3 : 6-Trichlorobenzaldoxime (20 g.), ethanol (100 c.c.), water (70 c.c.), and hydrochloric acid (*d* 1·16; 25 c.c.) were mixed and stirred, and zinc dust (20 g.) added during one hour. The temperature rose gradually to 40°. A further 40 c.c. of hydrochloric acid (*d* 1·16) were added in 10-c.c. portions to keep the reaction mixture strongly acid. The suspension was then heated to 60° for a few minutes, cooled, diluted with water, and filtered. The ethanol was removed from the filtrate by evaporation *in vacuo*, and the residue basified with sodium hydroxide solution. The oil which separated was extracted with ether, the ether removed from the dried ethereal solution, and the residue distilled *in vacuo*. The colourless oil (11 g.; b. p. 144°/12 mm.) gave a faintly turbid solution in dilute hydrochloric acid. It solidified on storage. It was dissolved in dilute hydrochloric acid, the solution treated with carbon and filtered, and the hydrochloride of the base precipitated by addition of sodium chloride. This was filtered off, dried, and dissolved in ethanol, the solution filtered, and the *hydrochloride* precipitated by addition of ether; it formed a white microcrystalline solid not melting below 270° (Found: C, 33·8; H, 2·7; N, 5·5. $C_7H_7NCl_4$ requires C, 34·0; H, 2·8; N, 5·7%). The base regenerated from the purified hydrochloride had m. p. 41—44° raised to 43—44° by crystallisation from light petroleum (b. p. 80—100°).

2 : 3 : 6-*Trichlorobenzyl Alcohol.*—2 : 3 : 6-Trichlorobenzylamine (20 g.) was dissolved in water (200 c.c.) and hydrochloric acid (*d* 1·16; 40 c.c.). Sodium nitrite (13·2 g.) was then added with stirring at 45°, precipitating a pale yellow gum. The mixture was cooled and extracted with ether, the ethereal solution dried, and the ether removed. The residue was distilled *in vacuo*, giving the *alcohol* (11 g.), b. p. 160—162°/12 mm., m. p. 60° raised by three recrystallisations from light petroleum (b. p. 80—100°) to 70—73° (constant) (Found: C, 40·0; H, 2·0; Cl, 50·5. $C_7H_5OCl_3$ requires C, 39·8; H, 2·4; Cl, 50·4%).

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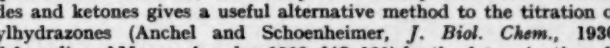
271. 1 : 2-*Dihydro*-2-*thianaphthalene Derivatives. Part I. Preparation and Reactions of* 1 : 2-*Dihydro*-1-*keto*-2-*thianaphthalenes.*

By D. J. Dijksman and G. T. Newbold.

Treatment of the rhodanine derivatives of *o*-carboxy-aldehydes and of an *o*-carboxy-ketone with sodium hydroxide gives 1 : 2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acids which can be decarboxylated to 1 : 2-dihydro-1-keto-2-thianaphthalenes. The sulphur atom in these thianaphthalenes (benzothiopyrans) is readily eliminated by ammonia and primary amines with the formation of *iso*quinoline derivatives.

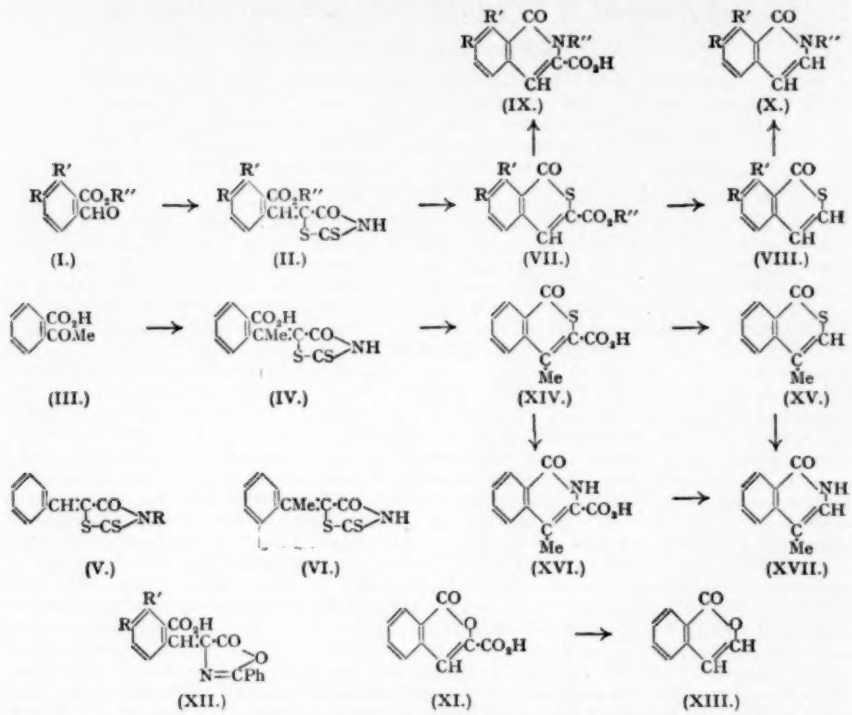
Though the condensation of rhodanine with aldehydes (Gränacher, *Helv. Chim. Acta*, 1922, **5**, 610, where references are given to earlier work; Gränacher, Gerö, Ofner, Klopfenstein, and Schlatter, *ibid.*, 1923, **6**, 458) and ketones (Brown, Bradsher, McCallum, and Potter, *J. Org. Chem.*, 1950, **15**, 174) has been extensively studied no record as far as we are aware exists of the condensation of *o*-carboxy-derivatives of aromatic aldehydes and ketones with rhodanine. We find that methyl phthalaldehydate (I; R = R′ = H, R″ = Me) and α-methyl opianate (I; R = R′ = OMe, R″ = Me) condense with rhodanine to give respectively 5-*o*-carbomethoxybenzylidene- (II; R = R′ = H, R″ = Me) and 5-(2′-carbomethoxy-3′ : 4′-dimethoxybenzylidene)-rhodanine (II; R = R′ = OMe, R″ = Me). Similarly phthaldehydic acid and 2-carboxyacetophenone (III) give the acids (II; R = R′ = R″ = H) and (IV) respectively; these products titrate to phenolphthalein as dibasic acids with sodium hydroxide, the second acidic function being present in the rhodanine moiety since we find that 5-benzylidene- (V; R = H) and 5-α-methylbenzylidene-rhodanine (VI) titrate sharply as monobasic acids under the same conditions. Holmberg (*J. pr. Chem.*, 1909, [ii], **79**, 266) determined the acidic strength of rhodanine as K_a^{25} 3 × 10^{-4} and showed that it can be titrated with sodium hydroxide by using phenolphthalein as indicator; the acidity of its readily accessible condensation products with aldehydes and ketones gives a useful alternative method to the titration of carboxy- or sulpho-phenylhydrazones (Anchel and Schoenheimer, *J. Biol. Chem.*, 1936, **114**, 539; Willstätter, Schuppli, and Mayer, *Annalen*, 1919, **418**, 121) for the determination of the molecular weights of carbonyl compounds. 5-Benzylidenerhodanine (V; R = H) with diazomethane gave only the 3-methyl derivative (V; R = Me), which has been obtained by Andreasch and Zipser (*Monatsh.*, 1904, **25**, 167) by condensation of benzaldehyde with 3-methylrhodanine. The methylation behaviour suggests that the principal acidic centre in 5-benzylidenerhodanine is the imino-group and this is supported by the identical spectral absorptions of (V; R = H and Me).

Condensation products of aromatic aldehydes with rhodanine have been used for the preparation of homologous acids (Julian and Sturgis, *J. Amer. Chem. Soc.*, 1935, **57**, 1126; Campbell and McKail, *J.*, 1948, 1251); the first step is hydrolysis to the β-aryl-α-thiopropionic acid by strong alkali (Gränacher, *loc. cit.*) :



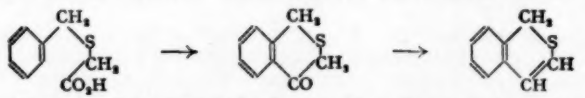
5-*o*-Carbomethoxybenzylidene- (II; R = R′ = H, R″ = Me) or 5-*o*-carboxybenzylidene-rhodanine (II; R = R′ = R″ = H) with hot sodium hydroxide solution gives an acidic product $C_{10}H_8O_3S$ which we formulate as 1 : 2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acid (VII; R = R′ = R″ = H), formed by loss of water from the intermediate *o*-carboxy-α-thiolcinnamic acid tautomeric with the β-*o*-carboxyphenyl-α-thiopropionic acid. Support for this formula comes from the formation of 1 : 2-dihydro-1-keto*iso*quinoline-3-carboxylic acid (IX; R = R′ = R″ = H) by treatment of the compound $C_{10}H_8O_3S$ with ethanolic ammonia. The acid (IX; R = R′ = R″ = H) has been prepared by Bamberger and Kitschelt (*Ber.*, 1892, **25**, 1138) by reaction of *iso*coumarin-3-carboxylic acid (XI) with ammonia and by alkaline hydrolysis of 5-*o*-carbomethoxybenzylidene-2-phenyloxazol-4-one (cf. XII; R = R′ = H) (Bain, Perkin, and Robinson, *J.*, 1914, 2392); in the latter reaction the ready cyclisation of the intermediate α-amino-*o*-carboxycinnamic acid to the *iso*quinoline parallels our method of formation of 1 : 2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acid. 1 : 2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acid reacts smoothly with methylamine, ethylamine, aniline, and benzylamine to give the corresponding *N*-substituted 1 : 2-dihydro-1-keto*iso*quinoline-3-carboxylic acids (IX; R = R′ = H, R″ = Me, Et, Ph, and CH_2Ph respectively), the first

three of which have been similarly obtained from *iso*coumarin-3-carboxylic acid (Bamberger and Frew, *Ber.*, 1894, **27**, 198). Both the *iso*coumarin-acid (Bamberger and Kitschelt, *loc. cit.*;



Zinke, *ibid.*, p. 1493) and 1 : 2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acid titrate normally with cold 0·1N-sodium hydroxide to phenolphthalein; heating them with excess of alkali, followed by hot back-titration, results in the uptake of two equivalents of alkali indicative of lactone ring opening.

1 : 2-Dihydro-4-keto-2-thianaphthalene has been prepared by cyclisation of benzylthioacetic acid (Lesser and Mehrlander, *Ber.*, 1923, **56**, 1642; von Braun and Weissbach, *ibid.*,



1929, **62**, 2416). Reduction of 1 : 2-dihydro-4-keto-2-thianaphthalene then led to 1 : 2-dihydro-2-thianaphthalene. No reference to 1-keto-derivatives of the latter compound appears in the literature to our knowledge. We have prepared 1 : 2-dihydro-1-keto-2-thianaphthalene (VIII; R = R′ = H) by decarboxylation of (VII; R = R′ = R″ = H); it has m. p. 78—79° and is similar in properties to *iso*coumarin (XIII) (m. p. 47°) (Bamberger and Frew, *loc. cit.*). Reaction of (VIII; R = R′ = H) with ammonia gives 1 : 2-dihydro-1-keto*iso*quinoline (X; R = R′ = R″ = H) as does similar treatment of (XIII) (Bamberger and Frew, *loc. cit.*). Unlike *iso*coumarin, 1 : 2-dihydro-1-keto-2-thianaphthalene does not reduce Fehling's solution.

5-(2′-Carbomethoxy-3′ : 4′-dimethoxybenzylidene)rhodanine (II; R = R′ = OMe, R″ = Me), when heated with sodium hydroxide, gives 1 : 2-dihydro-1-keto-7 : 8-dimethoxy-2-thianaphthalene-3-carboxylic acid (VII; R = R′ = OMe, R″ = H) which readily forms a methyl ester with diazomethane. Partial demethylation of the acid by constant-boiling hydrobromic

acid gives a monomethyl compound which we formulate as the 8-hydroxy-7-methoxy-compound (VII; R = OMe, R′ = OH, R″ = H) since opianic acid under similar conditions gives 2-formyl-6-hydroxy-5-methoxybenzoic acid (I; R = OMe, R′ = OH, R″ = H) (Wegscheider, *Monatsh.*, 1882, **3**, 356, 790; Liebermann, *Ber.*, 1896, **29**, 2030; Schorigin, Issaguljanz, and Below, *ibid.*, 1931, **64**, 274). 1 : 2-Dihydro-1-keto-7 : 8-dimethoxy-2-thianaphthalene-3-carboxylic acid can be decarboxylated in very low yield to give (VIII; R = R′ = OMe), and with ethanolic ammonia gives 1 : 2-dihydro-1-keto-7 : 8-dimethoxy*iso*quinoline-3-carboxylic acid (IX; R = R′ = OMe, R″ = H) identical with that prepared by Bain, Perkin, and Robinson (*loc. cit.*) by the oxazolone route from (XII; R = R′ = OMe). Reaction of (VII; R = R′ = OMe, R″ = H) with methylamine and ethylamine gives respectively the 2-methyl (IX; R = R′ = OMe, R″ = Me) and 2-ethyl (IX; R = R′ = OMe, R″ = Et) derivative of the *iso*quinoline-acid.

5-(*o*-Carboxy-α-methylbenzylidene)rhodanine (IV) is converted by alkali into 1 : 2-dihydro-1-keto-4-methyl-2-thianaphthalene-3-carboxylic acid (XIV) which readily forms 1 : 2-dihydro-1-keto-4-methyl*iso*quinoline-3-carboxylic acid (XVI) when heated with ethanolic ammonia. Decarboxylation of (XIV) proceeds smoothly with the formation of 1 : 2-dihydro-1-keto-4-methyl-2-thianaphthalene (XV), which with ammonia gives 1 : 2-dihydro-1-keto-4-methyl-*iso*quinoline (XVII) identical with the decarboxylation product of (XVI).

When the manuscript of this paper was complete, the communication of Kamal, Robertson, and Tittensor (*J.*, 1950, 3375) appeared, describing the conversion of 5-(6′-carbomethoxy-2′ : 4′-dimethoxybenzylidene)rhodanine into 1 : 2-dihydro-1-keto-5 : 7-dimethoxy-2-thianaphthalene-3-carboxylic acid by the method we have recorded above.

Experimental.

Rhodanine Condensation Products.—The method is exemplified by the preparation of 5-(2′-carbomethoxy-3′ : 4′-dimethoxybenzylidene)rhodanine. α-Methyl opianate (Bain, Perkin, and Robinson, *loc. cit.*; 10·0 g.) and rhodanine (6·0 g.) were dissolved in hot glacial acetic acid (30 c.c.), and powdered fused sodium acetate (12·0 g.) was added. After 30 minutes' heating under reflux dissolution was complete and the reaction mixture was poured into water (500 c.c.). The precipitated solid was crystallised from ethanol, giving 5-(*2′-carbomethoxy-3′ : 4′-dimethoxybenzylidene)rhodanine* (11·4 g., 75%) as yellow prisms, m. p. 191—193° (Found: C, 49·7; H, 4·2; N, 3·7; S, 18·4. $C_{14}H_{13}O_5NS_2$ requires C, 49·5; H, 3·9; N, 4·1; S, 18·9%). Light absorption in ethanol: Max. at 2610 (ε = 9100), 2850 (ε = 9900), 3020 (ε = 7900), 3100 (ε = 7400), and 3870 A. (ε = 37000).

5-*o-Carbomethoxybenzylidenerhodanine*, prepared from methyl phthalaldehydate in 60% yield, formed pale yellow needles (from ethanol), m. p. 215—216° (Found: C, 51·6; H, 3·5; N, 5·0; S, 22·3. $C_{12}H_9O_3NS_2$ requires C, 51·6; H, 3·2; N, 5·0; S, 23·0%). Light absorption in ethanol: Max. at 2610 (ε = 8800), 2780 (ε = 7600), and 3610 A. (ε = 27000).

5-*o-Carboxybenzylidenerhodanine*, prepared from phthalaldehydic acid in 74% yield, separated from aqueous ethanol as yellow needles, m. p. 265—266° (Found: C, 49·7; H, 3·0%; equiv., 134. $C_{11}H_7O_3NS_2$ requires C, 49·8; H, 2·7%; equiv., 132·5). Light absorption in ethanol: Max. at 2590 (ε = 7900), 2830 (ε = 8000) and 3600 A. (ε = 25200).

5-(*o-Carboxy-α-methylbenzylidene)rhodanine* was prepared from *o*-carboxyacetophenone [prepared by Gabriel and Michael's method, *Ber.*, 1877, **10**, 1554, by heating phthaloylacetic acid (14 g.) in water (70 c.c.) at 200° for 4 hours; yield 5·5 g., 45%; m. p. 114—115°] by the method described and crystallised from aqueous methanol as yellow needles, m. p. 192—194° (31% yield) (Found: C, 52·0; H, 3·7%; equiv., 141·5. $C_{12}H_9O_3NS_2$ requires C, 51·6; H, 3·2%; equiv., 139·5). Light absorption in ethanol: Max. at 2270 (ε = 8400), 2560 (ε = 8000), 2950 (ε = 11400), and 3460 A. (ε = 3300).

5-α-Methylbenzylidenerhodanine, prepared from acetophenone by the above method in 25% yield, separated from methanol as yellow needles, m. p. 166—167° (Brown, Bradsher, McCallum, and Potter, *J. Org. Chem.*, 1950, **15**, 174, give m. p. 165—166° for this compound prepared by condensation of acetophenone with rhodanine in the presence of ammonium chloride in aqueous ammonia) (Found: C, 56·2; H, 3·9%; equiv., 233. Calc. for $C_{11}H_9ONS_2$: C, 56·1; H, 3·9%; equiv., 235). Light absorption in ethanol: Max. at 2780 (ε = 9300) and 3530 A. (ε = 28500).

5-Benzylidenerhodanine, prepared by the method of Gränacher, Gerö, Ofner, Klopfenstein, and Schlatter (*loc. cit.*) (Found: equiv., 224. Calc. for $C_{10}H_7ONS_2$: equiv., 221), had light absorption in ethanol: Maxima at 2720 (ε = 10000) and 3740 A. (ε = 44000).

3-*Methylrhodanine* (cf. Andreasch and Zipser, *loc. cit.*).—Methyl *iso*thiocyanate (7·3 g.; *Org. Synth.*, **21**, 81) and mercaptoacetic acid (11·0 g.) in ethanol (20 c.c.) and water (10 c.c.) were refluxed for 2½ hours. Water (10 c.c.) was then added, the solution cooled, and the crystalline product collected (15·5 g.; m. p. 72—72·5; Andreasch and Zipser, *loc. cit.*, record m. p. 72°).

5-*Benzylidene-3-methylrhodanine.*—(*a*) Under the conditions prescribed by Andreasch and Zipser (*loc. cit.*) a very low yield was obtained. The following procedure is satisfactory. Benzaldehyde (3·0 g.), 3-methylrhodanine (3·8 g.), and fused sodium acetate (5·0 g.) were heated under reflux in acetic acid (15 c.c.) for 15 minutes. The hot solution from which solid had separated was poured into water and the product collected (4·5 g., 61%; m. p. 169°). 5-Benzylidene-3-methylrhodanine separated from methanol as light yellow needles, m. p. 169—170° (lit., m. p. 169°). Light absorption in ethanol: Max. at 2720 (ε = 12000) and 3750 A. (ε = 38000).

(*b*) 5-Benzylidenerhodanine (0·5 g.), suspended in methanol (10 c.c.), was treated with ethereal diazomethane (50 c.c., from 5 g. of nitrosomethylurea). Dissolution was rapidly effected with gas evolution, followed by separation of crystals. The solution was concentrated and the solid separated, having m. p. 162—164° (210 mg.). Crystallisation from methanol gave the 3-methyl derivative as light yellow needles, m. p. 169—170° undepressed by preparation (*a*) (Found : C, 56·2; H, 4·2. Calc. for $C_{11}H_9ONS_2$: C, 56·1; H, 3·9%).

1 : 2-*Dihydro*-1-*keto*-2-*thianaphthalene*-3-*carboxylic Acids*.—The carboxy- or carbomethoxy-rhodanine (0·01 mole) was heated with aqueous sodium hydroxide (20 c.c. ; 15%) for 30 minutes, the cooled solution poured into an excess of dilute hydrochloric acid, and the product collected. In this way 5-(2′-carbomethoxy-3′ : 4′-dimethoxybenzylidene)rhodanine gave 1 : 2-*dihydro*-1-*keto*-7 : 8-*dimethoxy*-2-*thianaphthalene*-3-*carboxylic acid* (75%) as yellow needles, m. p. 257—258° (from ethanol) (Found : C, 54·3; H, 4·0; S, 12·3%; equiv., 264. $C_{12}H_{10}O_5S$ requires C, 54·1; H, 3·8; S, 12·0%; equiv., 266). Light absorption in ethanol : Max. at 2460 (ε = 29500), 3320 (ε = 14600), 3700 (ε = 11300), and 3880 A. (ε = 10000). The *methyl* ester prepared by ethereal diazomethane separated from ethanol as light yellow laths, m. p. 152—153° (Found : C, 55·5; H, 4·4. $C_{13}H_{12}O_5S$ requires C, 55·7; H, 4·3%).

5-*o*-Carbomethoxybenzylidenerhodanine similarly gave 1 : 2-*dihydro*-1-*keto*-2-*thianaphthalene*-3-*carboxylic acid* (82%) prisms (from aqueous ethanol), m. p. 261—263° (Found : C, 58·6; H, 2·8%; equiv., 205. $C_{10}H_6O_5S$ requires C, 58·2; H, 2·9%; equiv., 206), also obtained from 5-*o*-carboxybenzylidenerhodanine as prisms (80% yield) (from aqueous ethanol), m. p. 261—263° undepressed by the foregoing preparation (Found : C, 58·5; H, 3·1%). Light absorption in ethanol : Max. at 2220 (ε = 29000), 2750 (ε = 5000), 3000 (ε = 7100), 3120 (ε = 7800), and 3470 (ε = 7600), inflection at 2450 A. (ε = 18500). The *methyl* ester, prepared by diazomethane, formed fine needles, m. p. 138—139°, from ethanol (Found : C, 59·9; H, 3·6. $C_{11}H_8O_5S$ requires C, 60·0; H, 3·7%).

5-(2′-Carboxy-α-methylbenzylidene)rhodanine gave 1 : 2-*dihydro*-1-*keto*-4-*methyl*-2-*thianaphthalene*-3-*carboxylic acid* (60%), needles, m. p. 243—245° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found : C, 60·1; H, 3·7%; equiv., 217. $C_{11}H_8O_5S$ requires C, 60·0; H, 3·7%; equiv., 220); light absorption in ethanol : Max. at 2480 (ε = 22400), 3000 (ε = 6300), and 3610 A. (ε = 4800). It forms a *methyl* ester which separates from methanol as fine felted needles, m. p. 152—154° (Found : C, 61·7; H, 4·3. $C_{12}H_{10}O_5S$ requires C, 61·5; H, 4·3%).

1 : 2-*Dihydro*-8-*hydroxy*-1-*keto*-7-*methoxy*-2-*thianaphthalene*-3-*carboxylic Acid*.—1 : 2-Dihydro-1-keto-7 : 8-dimethoxy-2-thianaphthalene-3-carboxylic acid (0·5 g.) was heated under reflux with constant-boiling hydrobromic acid (20 c.c.) during 3 hours. The cooled reaction mixture was filtered and the *product* (95% yield) crystallised from ethanol as needles, m. p. 304—305° (Found : C, 52·6; H, 3·5. $C_{11}H_8O_5S$ requires C, 52·4; H, 3·2%). An ethanolic solution of the compound gave a dark olive-green colour with aqueous ferric chloride.

1 : 2-*Dihydro*-1-*keto*-2-*thianaphthalene*.—1 : 2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acid (500 mg.) was heated at 330° for 10 minutes in a sublimation apparatus at atmospheric pressure. Sublimation was then carried out at 150°/0·5 mm. The sublimate was dissolved in ether and the ethereal solution washed with 2N-sodium hydroxide, then with water, and dried (Na_2SO_4). The alkaline washings on acidification gave unchanged acid (100 mg.). The ethereal extract was evaporated and the residue sublimed at 100°/0·5 mm., to give a yellow sublimate (230 mg., 41%), m. p. 77—78°. Two crystallisations from light petroleum (b. p. 60—80°) gave 1 : 2-*dihydro*-1-*keto*-2-*thianaphthalene* as needles, m. p. 78—79° (Found : C, 66·6; H, 3·7. C_9H_6OS requires C, 66·7; H, 3·7%). Light absorption in ethanol : Max. at 2130 (ε = 26300), 2430 (ε = 26000), 2650 (ε = 5400), 2850 (ε = 5000), and 3450 A. (ε = 4300). This substance is insoluble in water and soluble in the common organic solvents with the exception of light petroleum ; it dissolves in warm 2N-potassium hydroxide to give a colourless solution and does not reduce Fehling's solution on prolonged boiling.

1 : 2-*Dihydro*-1-*keto*-4-*methyl*-2-*thianaphthalene*.—1 : 2-Dihydro-1-keto-4-methyl-2-thianaphthalene-3-carboxylic acid (150 mg.) was heated at 310—315° for 10 minutes, then treated as in the last experiment, and the neutral fraction sublimed at 100°/0·5 mm. The pale yellow solid (80 mg.) had m. p. 71—74° ; it was dissolved in light petroleum (b. p. 60—80°) (25 c.c.) and adsorbed on a column (1 × 7 cm.) of alumina (Grade III). The column was washed with the same solvent (50 c.c.), evaporation of the combined eluates giving a negligible residue. Elution with benzene (50 c.c.) gave 60 mg. of crystalline material, m. p. 75—77°, still retaining a slight yellow colour not removed by crystallisation from light petroleum (b. p. 60—80°) from which the material separated as fine needles. A colourless product was obtained by two sublimations at 80°/0·5 mm., only the first two-thirds of the material being sublimed. 1 : 2-*Dihydro*-1-*keto*-4-*methyl*-2-*thianaphthalene* obtained in this way had m. p. 75—77° (Found : C, 68·4; H, 4·6. $C_{10}H_8OS$ requires C, 68·1; H, 4·5%). Yellow material gave consistently high C values. Light absorption in ethanol : Max. at 2170 (ε = 29000), 2470 (ε = 25000), 2680 (ε = 5500), 2870 (ε = 5000), 2990 (ε = 5000), and 3510 A. (ε = 4500).

1 : 2-*Dihydro*-1-*keto*-7 : 8-*dimethoxy*-2-*thianaphthalene*.—1 : 2-Dihydro-1-keto-7 : 8-dimethoxy-2-thianaphthalene-3-carboxylic acid (0·65 g.) was heated at 330° for 5 minutes at atmospheric pressure. The sublimate and residue were extracted with chloroform, and the extract was washed once with 2N-potassium hydroxide, then once with water, and dried (Na_2SO_4). The extract was evaporated and the residue sublimed at 180°/0·1 mm., to give a yellow gummy sublimate (65 mg.). This was dissolved in dry benzene (10 c.c.) and adsorbed on a column of alumina (Grade II ; 1 × 7 cm.). The column was washed with benzene–ether (1 : 1 ; 50 c.c.) and the eluate evaporated to give an almost colourless solid A (20 mg.). Further elution with the same solvent (50 c.c.) and evaporation of the eluate gave a solid B (15 mg.). Elution of the column with ether gave a negligible residue. Solid A, m. p. 85—90°, was sublimed at 100°/0·5 mm. and the sublimate crystallised from light petroleum (b. p. 80—100°) from which 1 : 2-*dihydro*-1-*keto*-7 : 8-*dimethoxy*-2-*thianaphthalene* separated as small needles, m. p. 92—94° (Found : C, 59·3; H, 4·6. $C_{11}H_{10}O_3S$ requires C, 59·5; H, 4·5%). Light absorption in ethanol : Max. at 2440 (ε = 20000), 2900 (ε = 4400), and 3800 A. (ε = 2200). Solid B, m. p. 148—150°, crystallised

from light petroleum (b. p. 80—100°) as fine needles, m. p. 152° (Found : C, 54·6; H, 4·2%). A mixture of the latter compound and 1 : 2-dihydro-1-keto-7 : 8-dimethoxy-2-thianaphthalene could be separated by sublimation at 100°/0·5 mm., only the latter subliming.

1 : 2-*Dihydro*-1-*keto*-7 : 8-*dimethoxy*isoquinoline-3-*carboxylic Acid.*—1 : 2-Dihydro-1-keto-7 : 8-dimethoxy-2-thianaphthalene-3-carboxylic acid (0·5 g.) in ethanolic ammonia (20 c.c.; saturated at 0°) was heated at 130° for 2½ hours. On cooling, the solid (0·45 g.) which separated was dissolved in water (1 c.c.) and the solution made acid to Congo-red with dilute hydrochloric acid. The precipitated *iso*quinoline-acid (0·40 g., 86%) crystallised from ethanol as fine needles, m. p. 256—257° undepressed by a sample of m. p. 257—258° prepared according to Bain, Perkin, and Robinson (*loc. cit.*) (Found : C, 58·1; H, 4·3; N, 5·7. Calc. for $C_{13}H_{11}O_5N$: C, 57·8; H, 4·4; N, 5·6%). Light absorption in ethanol : Max. at 2210 (ε = 26000), 3120 (ε = 16500), 3400 (ε = 11300), and 3450 A. (ε = 11300).

1 : 2-*Dihydro*-1-*keto*isoquinoline-3-*carboxylic Acid.*—By the above mothod 1 : 2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acid gave 1 : 2-dihydro-1-keto*iso*quinoline-3-carboxylic acid (90%) as fine needles (from ethanol), m. p. 326—328° undepressed by an authentic specimen (Bain, Perkin, and Robinson, *loc. cit.*) of the same m. p. (these authors and Bamberger and Kitschelt, *loc. cit.*, give m. p. 320°) (Found : C, 63·6; H, 3·3. Calc. for $C_{10}H_7O_3N$: C, 63·5; H, 3·7%). Light absorption in ethanol : Max. at 2240 (ε = 18600), 3010 (ε = 12500), and 3220 (ε = 8800), inflections at 2480 (ε = 8800) and 3360 A. (ε = 5600).

1 : 2-*Dihydro*-1-*keto*-4-*methyl*iso*quinoline*-3-*carboxylic Acid.*—This *acid* was obtained similarly (85%) as small needles, m. p. 335—336° (from ethanol) (Found : C, 65·5; H, 4·7. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·5%). Light absorption in ethanol : Max. at 2120 (ε = 20500), 2270 (ε = 14500), 2540 (ε = 5900), and 3070 (ε = 12200), inflection at 3250 A. (ε = 8200).

1 : 2-*Dihydro*-1-*keto*-7 : 8-*dimethoxy*-2-*methyl*iso*quinoline*-3-*carboxylic Acid.*—1 : 2-Dihydro-1-keto-7 : 8-dimethoxy-2-thianaphthalene-3-carboxylic acid (0·5 g.) was heated at 130° with aqueous methylamine (20 c.c.; 40%) and ethanol (20 c.c.) for 2 hours. The reaction mixture was concentrated and made acid (Congo-red) with dilute hydrochloric acid to give 1 : 2-*dihydro*-1-*keto*-7 : 8-*dimethoxy*-2-*methyl*-iso*quinoline*-3-*carboxylic acid monohydrate* (0·35 g., 72%) which crystallised from water as needles, m. p. 198—199° (Found : C, 55·1; H, 5·5. $C_{13}H_{13}O_5N,H_2O$ requires C, 55·5; H, 5·4%). Light absorption in ethanol : Max. at 2230 (ε = 39000), 3050 (ε = 12400), and 3460 A. (ε = 8500).

1 : 2-Dihydro-1-keto-2-methyl*iso*quinoline-3-carboxylic acid was obtained similarly (80%) from 1 : 2-dihydro-1-keto-2-thianaphthalene-3-carboxylic acid as fine needles (from water), m. p. 238—240° (Bamberger and Frew, *loc. cit.*, give m. p. 238°) (Found : C, 65·2; H, 4·1. Calc. for $C_{11}H_9O_3N$: C, 65·0; H, 4·5%). Light absorption in ethanol : Max. at 2240 (ε = 17000) and 2950 (ε = 10000), inflection at 3280 A. (ε = 8200).

2-*Ethyl*-1 : 2-*dihydro*-1-*keto*-7 : 8-*dimethoxy*isoquinoline-3-*carboxylic Acid.*—Reaction of 1 : 2-dihydro-1-keto-7 : 8-dimethoxy-2-thianaphthalene-3-carboxylic acid with ethylamine as above gave this *acid monohydrate* (70%) as pale yellow needles (from water), m. p. 128—130° (Found : C, 57·4; H, 5·4. $C_{14}H_{15}O_5N,H_2O$ requires C, 56·9; H, 5·8%). When this was dried at 70°/0·1 mm. the m. p. rose to *ca.* 160° and the specimen became gummy. Light absorption in ethanol : Max. at 2200 (ε = 33200), 3020 (ε = 11500) and 3500 A. (ε = 7700).

2-Ethyl-1 : 2-dihydro-1-keto*iso*quinoline-3-carboxylic acid was analogously obtained as small prisms, m. p. 200—201° (from water) (Bamberger and Frew, *loc. cit.*, give m. p. 202°) (Found : C, 66·6; H, 5·0. Calc. for $C_{13}H_{11}O_3N$: C, 66·3; H, 5·1%). Light absorption in ethanol : Max. at 2220 (ε = 18800) and 2980 (ε = 8600), inflection at 3270 A. (ε = 6300).

1 : 2-*Dihydro*-1-*keto*-2-*phenyl*iso*quinoline*-3-*carboxylic Acid.*—1 : 2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acid and boiling aniline gave 1 : 2-dihydro-1-keto-2-phenyl*iso*quinoline-3-carboxylic acid (85%) as small prisms (from aqueous ethanol), m. p. 272—273° (cf. Bamberger and Frew, *loc. cit.*, whose preparation from *iso*coumarin-3-carboxylic acid had m. p. 265°) (Found : C, 72·6; H, 3·9. Calc. for $C_{16}H_{11}O_3N$: C, 72·4; H, 4·2%).

2-*Benzyl*-1 : 2-*dihydro*-1-*keto*isoquinoline-3-*carboxylic Acid.*—1 : 2-Dihydro-1-keto-2-thianaphthalene-3-carboxylic acid (0·4 g.) was heated under reflux with benzylamine (5 c.c.) for 30 minutes. The cooled reaction mixture was poured into excess of dilute hydrochloric acid, and the precipitate (0·45 g.) collected. Crystallisation from aqueous ethanol gave 2-*benzyl*-1 : 2-*dihydro*-1-*keto*isoquinoline-3-*carboxylic acid* as small laths, m. p. 223—224° (Found : C, 73·1; H, 4·7. $C_{17}H_{13}O_3N$ requires C, 73·1; H, 4·7%). Light absorption in ethanol : Max. at 2060 (ε = 39000), 3010 (ε = 11500), and 3260 (ε = 6500), inflection at 2230 A. (ε = 26000).

1 : 2-*Dihydro*-1-*keto*-4-*methyl*isoquinoline.—(*a*) 1 : 2-Dihydro-1-keto-4-methyl-2-thianaphthalene (100 mg.) was heated with methanolic ammonia (15 c.c.; saturated at 0°) at 130° for 2 hours. The reaction mixture was evaporated to dryness and the residue crystallised from water from which 1 : 2-*dihydro*-1-*keto*-4-*methyl*isoquinoline (60 mg., 61%) separated as fine needles, m. p. 173—174° (Found : C, 75·7; H, 5·5. $C_{10}H_9ON$ requires C, 75·45; H, 5·7%). Light absorption in ethanol : Max. at 2250 (ε = 16200), 2850 (ε = 8900), and 3310 A. (ε = 5400).

(*b*) 1 : 2-Dihydro-1-keto-4-methyl*iso*quinoline-3-carboxylic acid (10 mg.) was heated to 340—350° until effervescence ceased and the residue was sublimed at 120°/10^{-4} mm. The sublimate (2 mg.) crystallised from water as fine needles, m. p. 172—173° alone or mixed with preparation (*a*).

1 : 2-*Dihydro*-1-*keto*isoquinoline(iso*Quinol*-1-*one*).—(*a*) 1 : 2-Dihydro-1-keto-2-thianaphthalene (100 mg.) was treated as in (*a*) in the previous experiment, to give 1 : 2-dihydro-1-keto*iso*quinoline (75 mg., 84%) as needles (from aqueous ethanol), m. p. 209° (Bamberger and Kitschelt, *loc. cit.*, give m. p. 208°) (Found : C, 75·0; H, 4·5. Calc. for C_9H_7ON : C, 74·5; H, 4·85%). Light absorption in ethanol : Max. at 2800 (ε = 9300) and 3240 A. (ε = 4900); Ewing and Steel, *J. Amer. Chem. Soc.*, 1946, **68**, 2181, give maxima at 2800 (ε = 8000) and 3250 A. (ε = 4500).

(*b*) 1 : 2-Dihydro-1-keto*iso*quinoline-3-carboxylic acid, when heated to 350°, gave 1 : 2-dihydro-1-keto*iso*quinoline as needles (from aqueous ethanol), m. p. 209—210° undepressed by preparation (*a*) (Found: C, 74·65; H, 4·5%).

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272. *Monosubstituted Pyrimidines, and the Action of Thiourea on Chloropyrimidines.*

By (MISS) M. P. V. BOARLAND and J. F. W. MCOMIE.

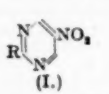
The amide and the methyl ester of pyrimidine-5-carboxylic acid, and the hydrochlorides of 4-chloro- and 4-mercapto-pyrimidine have been prepared. New syntheses of 2-mercapto- and of 5-amino-pyrimidine are also described. The reaction between certain chloropyrimidines and thiourea has been found to give good yields of the corresponding mercapto-compounds directly. Some of these results have been briefly reported elsewhere (*Chem. and Ind.*, 1950, 602).

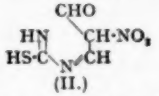
MANY polysubstituted pyrimidines have been prepared, mainly because of their relation to biologically important compounds, such as vitamin B_1, the purines, and pteridines (see review by Lythgoe, *Quart. Reviews*, 1949, **3**, 181). Certain compounds are used clinically, *e.g.*, barbiturates as hypnotics, and mercapto-compounds as antithyroid drugs (*Ann. Reports*, 1947, **44**, 247). Comparatively little is known about the parent compound and its monosubstitution products, except for 2-sulphanilamidopyrimidine, which is used in the chemotherapy of bacterial infections (Roblin *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 567).

Recently, attempts have been made to correlate the structure of polysubstituted pyrimidines with their infra-red (Brownlie, *J.*, 1950, 3062) and ultra-violet (Cavalieri and Bendich, *J. Amer. Chem. Soc.*, 1950, **72**, 2587) absorption spectra, but these attempts have been handicapped by the lack of suitable model compounds. We have undertaken the preparation of monosubstituted compounds for fundamental physical, chemical, and biological studies. The results of infra-red investigations on some of these compounds will be reported elsewhere by Dr. L. N. Short.

We have prepared pyrimidine-5-carboxylic acid by Gabriel and Colman's method (*Ber.*, 1904, **37**, 3643) and converted it into the amide and the methyl ester. These compounds are structurally analogous to nicotinic acid and its amide and might show growth-promoting or -inhibiting action on bacteria which require an exogenous source of these vitamins.

5-Aminopyrimidine has been prepared by a new route, involving the condensation of *S*-methylthiuronium sulphate with nitrosodiomalondialdehyde in the presence of 1-ethylpiperidine, giving 2-methylthio-5-nitropyrimidine (I; R = MeS). Other condensing agents such as pyridine, sodium hydroxide, diethylamine, and tetraethylammonium hydroxide were ineffective, while piperidine gave a mixture of the methylthio-compound and 5-nitro-2-


(I.)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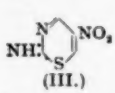
(III.)

piperidinopyrimidine (I; R = $C_5H_{10}N$). According to Hale and Brill (*J. Amer. Chem. Soc.*, 1912, **34**, 295) the condensation of thiourea with nitrosodiomalondialdehyde in the presence of small quantities of sodium hydroxide or diethylamine gave the thiourea (II), whereas the 1 : 3-thiazine (III) was obtained when piperidine was employed as condensing agent. We were not able to confirm these observations; in our hands the use of piperidine gave only the piperidino-derivative (I; R = $C_5H_{10}N$) and in no case could we obtain (II) and (III). The reduction of the nitro-group and hydrogenolysis of the methylthio-group of (I; R = MeS) were carried out in one stage by refluxing the compound in alcoholic solution with Raney nickel previously saturated with hydrogen. Another example of simultaneous reduction and desulphurisation is recorded by Cavalieri, Tinker, and Bendich (*J. Amer. Chem. Soc.*, 1949, **71**, 533) who obtained 4 : 5 : 6-triaminopyrimidine from 4 : 6-diamino-2-mercapto-5-nitrosopyrimidine.

In contrast to 3-aminopyridine, the action of nitrous acid on 5-aminopyrimidine does not

give a diazonium compound, nor could we isolate from the reaction mixture the still unknown 5-hydroxypyrimidine. Other routes for the preparation of the latter are being investigated.

In an attempt to prepare pyrimidine by the zinc dust reduction of 2 : 4-dichloropyrimidine in aqueous solution, a monochloropyrimidine was obtained (J. F. W. McOmie, Part II Thesis, Oxford, 1943). The orientation of this compound followed from its conversion into the known 2-anilino-derivative. The same partial reduction has since been reported by Matsukawa and Ohta (*J. Pharm. Soc., Japan*, 1950, **70**, 134). A similar result was obtained by Johnson and Joyce (*J. Amer. Chem. Soc.*, 1915, **37**, 2151), who found that 2 : 4-dichloro-5-ethoxypyrimidine gave the 2-chloro-5-ethoxy-compound with the same reducing agent. 2-Chloropyrimidine has also been prepared by the action of phosphorus oxychloride on 2-hydroxypyrimidine hydrochloride (B.P. Appln. 10,503/1949; Matsukawa and Ohta, *J. Pharm. Soc. Japan*, 1949, **69**, 491) and by the action of sodium nitrite on a solution of 2-aminopyrimidine in hydrochloric acid (U.S.P. 2,477,409/1949).

In contrast to the relatively stable 2-chloro-compound, 4-chloropyrimidine is extremely unstable and decomposes within a few minutes. Its hydrochloride, prepared by the action of phosphorus oxychloride on 4-hydroxypyrimidine, is, however, more stable, but can only be kept for a few days. A previous attempt to convert 4-hydroxy- into 4-chloro-pyrimidine was unsuccessful (Uber and Winters, *J. Amer. Chem. Soc.*, 1941, **63**, 137). Our method is essentially that of Mrs. R. H. Cornforth (private communication), who did not isolate the chloro-compound but converted it at once into 4-mercaptopyrimidine (see Experimental).

Until very recently three methods have been available for the synthesis of mercaptopyrimidines. The first of these, involving the condensation of thiourea with a β-dicarbonyl compound, is obviously limited to 2-mercaptopyrimidines. Again, the reaction of hydroxypyrimidines with phosphorus pentasulphide in inert solvents (Carrington, *J.*, 1944, 124) has only limited application, while the more general method of treating chloropyrimidines with alkali hydrogen sulphides often involves drastic conditions resulting in low yields (Gabriel and Colman, *Ber.*, 1899, **32**, 2921). We have found that some chloropyrimidines react with thiourea in boiling alcohol to give good yields of the corresponding thiols directly, no intermediate products being isolated. Thus 2-chloro- and 2 : 4-dichloro-pyrimidines gave the 2-mercapto- and 2 : 4-dimercapto-compounds in 50 and 90% yields, respectively, while 4-chloropyrimidine hydrochloride gave a 70% yield of 4-mercaptopyrimidine hydrochloride. Since the completion of this work Polonovski and Schmitt (*Bull. Soc. chim.*, 1950, **17**, 616) have described the reaction of polysubstituted chloropyrimidines with thiourea under somewhat milder conditions. In most cases they obtained the corresponding thiuronium salts which they were able to hydrolyse to the mercapto-compounds. From 2-amino-6-chloro-4-methylpyrimidine they could only isolate the dipyrimidyl sulphide.

Reaction of thiourea with 2-chloro-4 : 6-dimethylpyrimidine in hot alcohol gave mainly the corresponding thiuronium chloride, together with an unidentified compound (see Experimental). Alkaline hydrolysis of the former, under conditions similar to those used by Polonovski and Schmitt, yielded the expected mercapto-compound.

From the reaction between 2 : 4 : 6-trichloropyrimidine and thiourea in hot alcohol we obtained intractable products similar to those obtained by Polonovski and Schmitt (*loc. cit.*). Alkaline hydrolysis failed to give 2 : 4 : 6-trimercaptopyrimidine.

The number of heterocyclic halides reported to react with thiourea to give the corresponding mercapto-compounds directly is quite small. Rosenhauer, Hoffmann, and Heuser (*Ber.*, 1929, **62**, 2730) showed that α-chloro-quinoline and -lepidine and their methiodides reacted in boiling alcohol to give the corresponding α-mercapto-derivatives. When the reaction was carried out at room temperature, the intermediate thiuronium salts could be isolated. Scott and Watt (*J. Org. Chem.*, 1937, **2**, 148) obtained theoretical yields of 2-mercapto- and 2-mercapto-6-nitrobenzthiazoles from the corresponding chlorides. They could not isolate thiuronium salts even when the reaction was carried out in the cold. The majority of heterocyclic halides react with thiourea to give thiuronium salts or sulphides (*e.g.*, see Renfrew, *J. Amer. Chem. Soc.*, 1946, **68**, 1433; Surrey and Lindwall, *ibid.*, 1940, **62**, 1697). Sulphides are frequently formed both in the initial reaction and during the hydrolysis of the thiuronium salts. A summary of these reactions and the mechanisms put forward to explain them is given by Polonovski and Schmitt (*loc. cit.*). Although there does not appear to be any obvious connection between the structure of the heterocyclic halide and the reaction product, the experimental conditions seem to have an important bearing on the course of the reaction. In general, prolonged heating favours thiol formation, and sulphides appear to be formed more readily in aqueous media (see, *e.g.*, Watt, *J. Org. Chem.*, 1939, **4**, 436). A further example of the thermal effect is afforded by 2-bromo-

pyridine, which readily gives the thiuronium salt, but on prolonged heating under reflux gives a small yield of 2-mercaptopyridine. The latter has been prepared by Phillips and Shapiro (*J.*, 1942, 584) by the hydrolysis of the thiuronium salt, which they did not isolate. 3-Bromopyridine was recovered unchanged after 24-hours refluxing with thiourea in alcohol.

Experimental.

(M. p.s are uncorrected. Microanalyses are by Mr. W. M. Eno, Bristol, and Drs. Weiler and Strauss, Oxford.)

Methyl Pyrimidine-5-carboxylate.—A solution of pyrimidine-5-carboxylic acid (2·07 g.) (Gabriel and Colman, *Ber.*, 1904, **37**, 3643) in methanol (50 c.c.) saturated with dry hydrogen chloride was kept for 3 days. After removal of the solvent, the residue was made just alkaline by addition of aqueous sodium carbonate, and the solution extracted with ether (4 × 50 c.c.). The combined, dried extracts yielded a brown solid (1·22 g.), m. p. 67—68°, which was sublimed at 60°/20 mm., giving pure *methyl pyrimidine-5-carboxylate* (1·1 g., 48%), m. p. 84—85° (Found: C, 52·3; H, 4·3; N, 20·6. $C_6H_6O_2N_2$ requires C, 52·2; H, 4·35; N, 20·3%). The ester is readily soluble in water, methanol, and ether, and sparingly soluble in ethyl acetate.

Pyrimidine-5-carbonamide.—(*a*) Methyl pyrimidine-5-carboxylate (0·5 g.) and aqueous ammonia (*d*, 0·88; 20 c.c.) were kept for 2 days with occasional shaking. The white crystalline solid (0·2 g.; m. p. 209—213°) was collected and dried on the water-bath. Sublimation at 140°/20 mm. gave the pure *amide* (0·15 g., 34%), m. p. 211—213° (Found: C, 48·9; H, 4·1. $C_5H_5ON_3$ requires C, 48·8; H, 4·1%). (*b*) Methyl pyrimidine-5-carboxylate (0·44 g.) in methanol (10 c.c.) saturated with dry ammonia was kept for 4 days. The crude amide (0·29 g.) was purified by sublimation giving the pure material (0·25 g., 64%), m. p. 210—213°. (*c*) The amide was also prepared in low yield by the action of aqueous ammonia (*d* 0·88) on the acid chloride prepared by treatment of pyrimidine-5-carboxylic acid with thionyl chloride.

2-Methylthio-5-nitropyrimidine.—A mixture of methylthiuronium sulphate (3·6 g.), nitrosodiomalondialdehyde (4·0 g.) (Hill and Torry, *Amer. Chem. J.*, 1899, **22**, 89), and 1-ethylpiperidine (3·0 g.) in water (50 c.c.) was kept at 60° for 15 minutes. Next day, the solid was collected and sublimed at 80°/0·5 mm. (1·15 g., 26·4%). After two further sublimations *2-methylthio-5-nitropyrimidine* was obtained as very pale yellow needles, m. p. 82—83° (Found: C, 35·2; H, 3·0; N, 24·3; S, 17·1, 19·6. $C_5H_5O_2N_3S$ requires C, 35·1; H, 2·9; N, 24·6; S, 18·7%).

5-Aminopyrimidine.—Freshly prepared Raney nickel (40·0 g. of an ethanolic suspension) (Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353) in dry ethanol (50 c.c.) was saturated with hydrogen (*ca.* 35 c.c.) at atmospheric pressure and temperature. 2-Methylthio-5-nitropyrimidine (4·3 g.) in ethanol (150 c.c.) was added and the suspension refluxed for 3 hours with vigorous stirring. After filtration the solution was evaporated to dryness under reduced pressure, leaving a pale brown crystalline product (1·8 g., 75·4%). Several recrystallisations from benzene gave pure 5-aminopyrimidine as fine needles, m. p. 170—171° (Found: C, 50·8; H, 5·1; N, 44·3. Calc. for $C_4H_5N_3$: C, 50·5; H, 5·3; N, 44·2%). Roblin, Winnek, and English (*J. Amer. Chem. Soc.*, 1942, **64**, 567) give m. p. 170—171° (corr.).

5-Nitro-2-piperidinopyrimidine.—A mixture of thiourea (0·24 g.), nitrosodiomalondialdehyde (0·5 g.), and piperidine (0·26 g.) in water (10 c.c.) was kept at 70° for 10 minutes. After 12 hours the yellow crystalline product was collected (0·1 g., 15·3%). *5-Nitro-2-piperidinopyrimidine* crystallised from ethanol in shining yellow plates, m. p. 147—148° (Found: C, 52·4; H, 5·7; N, 26·6. $C_9H_{12}O_2N_4$ requires C, 52·0; H, 5·75; N, 26·9%).

2 : 4-Dichloropyrimidine.—Hilbert and Johnson's method (*J. Amer. Chem. Soc.*, 1930, **52**, 1154) was improved by the use of dimethylaniline (cf. Baddiley and Topham, *J.*, 1944, 678). Uracil (40·0 g.) was added portionwise to a mixture of dimethylaniline (46 c.c.) and phosphorus oxychloride (80·0 g.). The mixture was refluxed for 5 minutes and the dark brown liquid poured on ice (600 g.). The deep purple solution was filtered and extracted with ether (5 × 200 c.c.); the combined, dried extracts gave crystalline 2 : 4-dichloropyrimidine (30·4 g., 57%).

Reduction of 2 : 4-Dichloropyrimidine.—2 : 4-Dichloropyrimidine (14·0 g.), followed by zinc dust (66·6 g.), was added to a vigorously stirred, boiling solution of ammonium chloride (6·6 g.) in water (666 c.c.). After half an hour more zinc dust (13·6 g.) was added and boiling continued for another 1½ hours. After filtration the solution was distilled until *ca.* 500 c.c. of distillate had been collected; this was saturated with sodium chloride and continuously extracted with ether for 16 hours. Removal of the ether from the dried extract gave 2-chloropyrimidine (3·1 g.) as brownish crystals, m. p. 61°. The pure compound was obtained in the form of colourless needles, m. p. 63·5—64°, by sublimation at 50°/18 mm. (Found: C, 42·0; H, 2·8; N, 24·7; Cl, 30·0. Calc. for $C_4H_3N_2Cl$: C, 42·0; H, 2·6; N, 24·5; Cl, 31·0%). The mercuric chloride complex separated as colourless needles.

When 2-chloropyrimidine (0·1 g.) was warmed on a water-bath with excess of aniline (1·0 c.c.) and the mixture left overnight, crystalline 2-anilinopyrimidine separated. After crystallisation from aqueous ethanol and aqueous methanol, the pure compound was obtained as white needles, m. p. 115·5—116° (Found: C, 70·0; H, 5·25. Calc. for $C_{10}H_9N_3$: C, 70·2; H, 5·3%). Johnson and Heyl (*Amer. Chem. J.*, 1907, **38**, 237) give m. p. 116°.

4-Chloropyrimidine Hydrochloride.—4-Hydroxypyrimidine (1·0 g.) [obtained in 80% yield by Brown's method (*J. Soc. Chem. Ind.*, 1950, **69**, 353)] was treated with phosphorus oxychloride (4·0 c.c.) at 100° until dissolution occurred (*ca.* 5 minutes), the reaction being carried out in the test-tube portion of a "cold-finger" sublimation apparatus. The product was washed with light petroleum (b. p. 40—60°), the "cold-finger" condenser inserted, and the pressure slowly reduced. At 90°/20 mm. a white crystalline product began to sublime and sublimation proceeded rapidly at 130°/20 mm. The crude material (0·4 g., 25·4%) melted with decomposition over the range 158—170°. After further sublimation, *4-chloropyrimidine hydrochloride* decomposed when heated to 193—194° in a sealed tube (Found: C, 32·1; H, 3·0; N, 18·3; Cl, 48·4. $C_4H_3N_2Cl,HCl$ requires C, 31·8; H, 2·6; N, 18·5; Cl, 47·0%).

4-Chloropyrimidine hydrochloride was found to be readily soluble in water and ethanol. The mercuric chloride complex separated from an aqueous solution as fine needles. The hydrochloride is, however, unstable, decomposing after a few days to a bright yellow solid; its vapour is lachrymatory and the substance has an irritating effect on the skin.

4-Chloropyrimidine was liberated from the hydrochloride by treatment with aqueous potassium carbonate in the presence of ether. It was obtained as an oil, which decomposed within a few minutes to an orange ether-insoluble solid.

2-Mercaptopyrimidine.—A mixture of 2-chloropyrimidine (1·0 g.) and thiourea (0·9 g.) in ethanol (40 c.c.) was refluxed for 10½ hours, the initially colourless solution becoming yellow after about 5 hours. After concentration, 2-mercaptopyrimidine separated in the form of greenish-yellow plates (0·5 g., 50%). The pure compound, m. p. 230° (decomp.; bath preheated to 220°), was obtained by sublimation at 120°/20 mm. (Found: C, 42·8; H, 3·7; N, 24·8; S, 28·2. Calc. for $C_4H_4N_2S$: C, 42·8; H, 3·6; N, 25·0; S, 28·6%). Roblin and Clapp (*J. Amer. Chem. Soc.*, 1950, **72**, 4890) record m. p. 220° (decomp.).

2-Mercaptopyrimidine is soluble in methanol, moderately soluble in water and ethanol, and very sparingly soluble in chloroform.

4-Mercaptopyrimidine Hydrochloride.—A mixture of 4-chloropyrimidine hydrochloride (0·1 g.) and thiourea (0·07 g.) in ethanol (20 c.c.) was refluxed for 2 hours. The solution became bright yellow as soon as it was warmed. When the solution was concentrated, bright yellow needles separated (0·07 g., 70%). After sublimation at 130°/20 mm., *4-mercaptopyrimidine hydrochloride* had m. p. 220° (decomp.) (Found: C, 32·6; H, 3·7; N, 18·4; S, 22·0. $C_4H_4N_2S$,HCl requires C, 32·3; H, 3·4; N, 18·8; S, 21·6%).

4-Mercaptopyrimidine, liberated from the hydrochloride by treatment with aqueous ammonia, was obtained as yellow needles, m. p. 187°. Mrs. Cornforth (private communication) found m. p. 188° for this compound, prepared by the action of sodium hydrogen sulphide on crude 4-chloropyrimidine hydrochloride.

Reactions of Thiourea.—(i) *With 2 : 4-dichloropyrimidine.* A mixture of 2 : 4-dichloropyrimidine (2·0 g.) and thiourea (2·5 g.) in ethanol (70 c.c.) was refluxed for 2 hours, the colour gradually becoming bright yellow. Crystalline 2 : 4-dithiouracil (1·8 g., 90%) separated after the solution had been concentrated. Recrystallisation from water gave the pure material as shining yellow needles, m. p. 285° (decomp.) (Found: C, 33·8; H, 2·8; N, 19·5; S, 45·0, 43·7. Calc. for $C_4H_4N_2S_2$: C, 33·4; H, 2·8; N, 19·4; S, 44·5%). The m. p. was not depressed by mixture of the specimen with a sample prepared by the method described by Wheeler and Liddle (*Amer. Chem. J.*, 1908, **40**, 557).

(ii) *With 2-chloro-4 : 6-dimethylpyrimidine.* A mixture of 2-chloro-4 : 6-dimethylpyrimidine (6·0 g.), prepared by Matsukawa and Ohta's method (*J. Pharm. Soc., Japan*, 1949, **69**, 491), and thiourea (3·2 g.) in ethanol (120 c.c.) was refluxed for 6 hours and the yellow solution slightly concentrated. Next day a small quantity (1·3 g.) of a bright yellow product was collected. After several recrystallisations from ethanol the pure material was obtained as shining, yellow plates, m. p. *ca.* 198° (decomp.) (Found: C, 44·0; H, 5·2; N, 22·1; S, 18·7; Cl, 10·6. $C_{11}H_{15}N_5S_2$,HCl requires C, 43·8; H, 4·9; N, 21·3; S, 19·4; Cl, 10·8%). The structure of this *compound* has not yet been established. The main product of the reaction was obtained after further concentration of the mother liquor, and separated as pale yellow needles (6·3 g.). After recrystallisation from ethanol–ether (*4 : 6-dimethyl-2-pyrimidyl)thiuronium chloride* was obtained as almost colourless needles, m. p. *ca.* 191° (decomp.) (Found: C, 38·9; H, 4·9; N, 25·9. $C_7H_{11}N_4SCl$ requires C, 38·5; H, 5·0; N, 25·65%).

Hydrolysis of (4 : 6-dimethyl-2-pyrimidyl)thiuronium chloride. A solution of the thiuronium salt (2·0 g.) in N-sodium hydroxide (40 c.c.) was refluxed for ½ hour. After acidification with acetic acid and concentration, the solution deposited 2-mercapto-4 : 6-dimethylpyrimidine as shining, orange needles (0·7 g.), m. p. 208—210°. Sublimation at 140°/0·5 mm. gave the pure compound as pale yellow needles, m. p. and mixed m. p. with an authentic sample 208—210° (Found: C, 51·8; H, 5·65; N, 19·9; S, 22·8. Calc. for $C_6H_8N_2S$: C, 51·5; H, 5·2; N, 20·0; S, 22·8%). Hale and Williams (*J. Amer. Chem. Soc.*, 1915, **37**, 594) give m. p. 210°. Treatment of an ethanolic solution of the mercapto-compound with dilute hydrochloric acid intensified the yellow colour, and addition of ether precipitated a hydrochloride as long, yellow needles, m. p. 260° (decomposing >240°). The m. p. was not depressed by admixture of the hydrochloride with 2-mercapto-4 : 6-dimethylpyrimidine hydrochloride prepared under the same conditions.

(iii) *With 2-bromopyridine.* (*a*) A mixture of 2-bromopyridine (3·0 g.) and thiourea (1·5 g.) in ethanol (30 c.c.) was refluxed for 1 hour. After concentration of the yellow solution, pale yellow crystals were obtained (2·4 g.). Recrystallisation from ethanol–ether gave pure *2-pyridylthiuronium bromide* as needles, m. p. 126—127° (Found: C, 30·6; H, 3·5; N, 17·9. $C_6H_8N_2SBr$ requires C, 30·8; H, 3·4; N, 17·9%).

Hydrolysis of the thiuronium salt with concentrated ammonia solution by the method described by Phillips and Shapiro (*J.*, 1942, 584) gave 2-mercaptopyridine as yellow prisms, m. p. 125° after recrystallisation from benzene. Marckwald, Klemm, and Trabert (*Ber.*, 1900, **33**, 1556) give m. p. 125°.

(*b*) A mixture of 2-bromopyridine (6·0 g.) and thiourea (3·0 g.) in ethanol (80 c.c.) was boiled under reflux for 24 hours. The bright yellow solution was concentrated and the remainder of the ethanol removed under reduced pressure, leaving a yellow syrup. This was dissolved in a little water, and the aqueous solution saturated with sodium chloride and extracted many times with ether. Removal of the ether from the dried extract left an oil which, when triturated with a little cold ether, gave 2-mercaptopyridine (50 mg.) as bright yellow prisms, m. p. 123—125° alone or mixed with the product from the hydrolysis of the thiuronium salt.

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THE UNIVERSITY, BRISTOL. [*Received, February 3rd*, 1951.]

273. *The Crystal Structure of Cupric Tropolone and the Dimensions of the Tropolone Ring.*

By J. Monteath Robertson.

A two-dimensional crystal analysis of cupric tropolone has been carried out, making use of the phase-determining power of the copper atom. The analysis is practically a direct one from the *X*-ray measurements, and makes only a minimum of reference to the chemical structure. In the final projection, made by the usual Fourier series method, all the atoms (except hydrogen) are clearly resolved, and the bond lengths and angles are worked out. The tropolone ring appears to be an almost regular planar heptagon, with an average carbon–carbon distance of 1·40 A., indicating strong aromatic character. It is possible to differentiate the oxygen atoms as carbonyl and hydroxyl on the basis of bond-length measurements. The central cupric copper is coplanar with its four surrounding oxygen atoms, which lie approximately at distances to be expected for covalent linkages of the dsp^2 type.

The chemistry of tropolone and some of its derivatives has been described by Cook, Gibb, Raphael, and Sommerville (*J.*, 1951, 503) and the infra-red spectrum has been studied by Koch (*J.*, 1951, 512). One point of outstanding interest in these structures which cannot be completely solved by organic chemical methods concerns the fine structure of the seven-membered carbon ring. The evidence available from various chemical and physical methods of approach has been fully discussed in the above references, but no rigorous determination of the molecular geometry has been made. It is obviously desirable to measure the spatial positions of the atoms in these molecules as precisely as possible. The most feasible and indeed the only way of doing this with certainty for structures of this degree of complexity is by means of the *X*-ray crystallographic method. We have, therefore, commenced such investigations on tropolone and a number of its derivatives.

The present paper describes the results obtained for the copper complex, known as cupric tropolone. This derivative was chosen for the initial study for the following reasons. The crystals, although small, are extremely stable. They are monoclinic, and one axis (*c*) is as short as 3·8 A. It should, therefore, be possible to obtain a clear projection of the whole structure in this direction, as any interleaving of the molecules within this periodicity is clearly ruled out. The copper atoms are also found to lie at symmetry centres in the structure, and, for those *X*-ray reflections to which they contribute, the copper atoms should to a very large extent be phase determining. This opens up the possibility of a perfectly direct approach to the structure, without making use of any of the chemical evidence.

The whole situation is clearly analogous to the metal phthalocyanine crystal structures (Robertson, *J.*, 1935, 615; 1936, 1195; Robertson and Woodward, *J.*, 1937, 219; 1940, 36). In nickel phthalocyanine it was found that the phase constants of 132 of the 152 ($h0l$) reflections were governed by the central nickel atom, while in platinum phthalocyanine all the 302 ($h0l$) reflections were phase determined. As the molecule of cupric tropolone is very much smaller than the nickel phthalocyanine molecule ($C_{14}H_{10}O_4Cu$ as against $C_{32}H_{16}N_8Ni$) it is reasonable to expect that all or nearly all of the corresponding phase constants in the cupric tropolone structure will be determined by the copper atom.

There is, however, one important difference. In the phthalocyanine structures the short axis is the monoclinic symmetry axis *b*. Consequently, the principal projections, which give practically all the information about the structure and in which all the atoms are resolved, are compounded from the ($h0l$) structure factors, to all of which the central metal atom makes a positive contribution. In projection the metal atom lattice is effectively primitive. In cupric tropolone, however, the short axis is the monoclinic axis *c* and the principal projection is compounded from the ($hk0$) structure factors. Here the copper atoms only contribute to those structure factors for which the index sum ($h + k$) is even, because in this projection the metal atom lattice is face-centred. For the structure factors with ($h + k$) odd, the contributions from the copper atoms cancel each other out, and consequently these reflections are not phase determined.

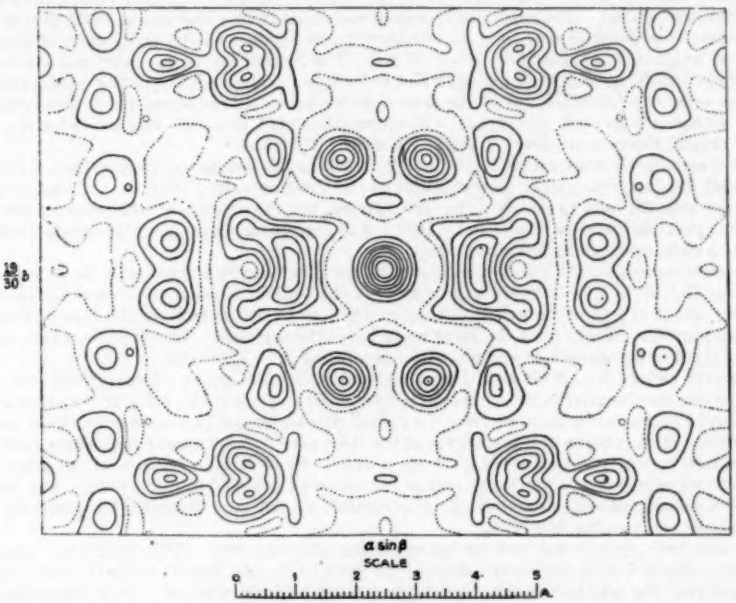
It is, of course, true that these cases are both present in the phthalocyanine structure, but here the *a* and *c* projections are of no practical importance because the atoms are not resolved.

Consequently, the problem was not fully studied at that time. (Since then, however, various projections in analogous structures have been studied in some detail; *e.g.*, strychnine sulphate and selenate, Bokhoven, Schoone, and Bijvoet, *Proc. K. Acad. Sci. Amsterdam*, 1947, **50**, 825; 1948, **51**, 990.) Conversely, in cupric tropolone, the projection of the structure along the symmetry axis *b* will be completely phase determined, but this projection is not likely to prove a useful one.

The solution of the cupric tropolone structure, described below, is therefore of some crystallographic interest, as a supplement to the earlier phthalocyanine studies, as well as of chemical interest in relation to the geometry of the molecule.

FIG. 1.

Projection along c, *synthesised from* (h + k)*-even structure factors only. It shows the structure superimposed on its mirror image. The contour scale is arbitrary, but it is reduced by a factor of* 5 *on the central atom.*



The analysis proceeds in two stages. The first is perfectly direct and independent of any chemical information, making use of the phase-determined reflections only. This gives a picture of the structure superimposed on a mirror image of itself (Fig. 1). From the co-ordinates so obtained the phases of the remaining reflections can then be determined, and the analysis carried to completion (Fig. 2). At the beginning of this second stage, it is convenient, but not absolutely essential, to make reference to the expected chemical structure as an aid in separating the molecule from its superimposed mirror image.

As the analysis, limited by the shape and size of the crystals, is at present confined to two dimensions, only two co-ordinates for each atom can be determined directly. It is shown, however, that the projections of the tropolone ring so obtained conform very accurately to the projection of a regular planar heptagon, and on this basis the bond lengths and angles are worked out. The average value of the carbon–carbon bond length in the ring is 1·40 Å., and deviations from this value are so small that they may be due to errors in measurement, although there is some evidence of a faint alternation of long and slightly shorter bonds in the ring. These dimensions are typically aromati cin character. The cupric copper atom is coplanar with its four surrounding oxygen atoms which lie approximately in the positions to be expected for covalent linkages of the dsp^2 coplanar type. The oxygen atoms can, however, be differentiated

by the lengths of the links which they make to the ring carbon atoms (1·25 and 1·34 A.) as belonging to the carbonyl and the hydroxyl type respectively.

Crystal Data.—Cupric tropolone, $(C_7H_5O_2)_2Cu$; M, 305·8; m. p. (decomp.) 300°; d, calc. 1·683, found 1·696. Monoclinic prismatic, $a = 11·60 \pm 0·05$, $b = 13·82 \pm 0·02$, $c = 3·80 \pm 0·005$ A., $\beta = 93°$ (approx.). Absent spectra, $(h0l)$ when h is odd (not fully established), $(0k0)$ when k is odd. Space group, C_{2h}^5–$P2_1/a$. Two molecules per unit cell. Molecular symmetry, centre. Volume of the unit cell = 608 A.^{3}. Total number of electrons per unit cell = F(000) = 310.

This copper derivative crystallises in very fine lustrous green needles from benzene or alcohol. The system is monoclinic and the needle axis has been chosen as the c axis. A pair of (110) faces are usually well developed, with very small (100) or (010) faces. Small end faces are sometimes visible, but could not be positively identified.

Experimental Measurements.—Copper-$K\alpha$ radiation was used ($\lambda = 1·542$ A.), and the reflections were recorded on rotation, oscillation, and moving-film photographs. Owing to the needle-like shape of the crystals, satisfactory moving-film records could only be obtained for the $(hk0)$ zone reflections. The principal specimen employed in this case had a width of 0·09 mm., a thickness of 0·05—0·06 mm., and an effective length (limited by the collimator) of about 0·9 mm.; it weighed approximately $6·8 \times 10^{-4}$ g. The intensities of the $(hk0)$ reflections were estimated visually by using the multiple-film technique. The small size of the crystal rendered accurate estimation difficult, but at the same time tended to reduce errors due to absorption, for which no corrections were attempted. F values calculated from the intensities by the usual mosaic crystal formulæ are listed in Table IV under " F, meas."

The a and b periodicities were established by rotation and oscillation photographs, the needle axis being kept approximately perpendicular to the rotation axis. With the crystals available it was not possible fully to establish the $(h0l)$ halving, but the absence of odd orders of $(h00)$ and $(0k0)$ was checked as far as 14,0,0 and 0,16,0. Any remaining space-group uncertainty will not affect the main conclusions described below.

Structure Analysis.—As the unit cell contains two copper atoms, these must lie on symmetry centres at (0,0,0), $(\frac{1}{2},\frac{1}{2},0)$. When $(h + k)$ is even the contributions of the copper atoms will be in phase, and it is safe to assume that these contributions will determine the sign of the total structure amplitude for at least the great majority of these planes. We may, therefore, assume that the $(hk0)$ structure factors are of positive sign when $(h + k)$ is even.

However, when $(h + k)$ is odd, the contributions of the copper atoms cancel out. The structure factors observed in this case are therefore due to the contributions of the other atoms, carbon and oxygen, in the molecule, and the sign of these structure factors may be either positive or negative. This is borne out by a survey of the $(hk0)$ zone of reflections, which shows that these are generally much stronger when $(h + k)$ is even; 91 of these even-index reflections were observed out of a possible 111 lying within the range of copper radiation (82%), but only 28 odd-index reflections were observed out of a possible 97 (29%). Overall, 119 reflections were observed out of a possible 208 (57%).

The structure analysis was now carried out in the following way. A double Fourier synthesis was first performed with the even-index ($h + k$ even) structure factors as coefficients, with all signs positive, the odd-index structure factors being entirely omitted. It is clear that this operation introduces a false element of symmetry into the resulting projection, which consists of a two-fold axis or plane, parallel to a or b, passing through the symmetry centres, the effect being to create a face-centred projection. Such a projection must result from the imposed general halving when $(h + k)$ is odd. In this projection the peak density of each atom will be halved and each will be accompanied by its mirror image. To obtain the real structure it will be necessary to select one atom from each of the resulting pairs and reject the other.

The result of this synthesis, from the even-index structure factors alone, is shown in Fig. 1. It is, of course, produced directly from the X-ray measurements by application of the usual standard calculations, and involves no knowledge of the chemical structure. No atoms have been assumed to exist in the structure apart from the central metal atom.

The next step, however, is accomplished more easily by making some reference to the known chemical facts.* It is necessary to select one atom from each of the pairs and reject the other, making use of the co-ordinates of the selected atoms to calculate the phase constants of the

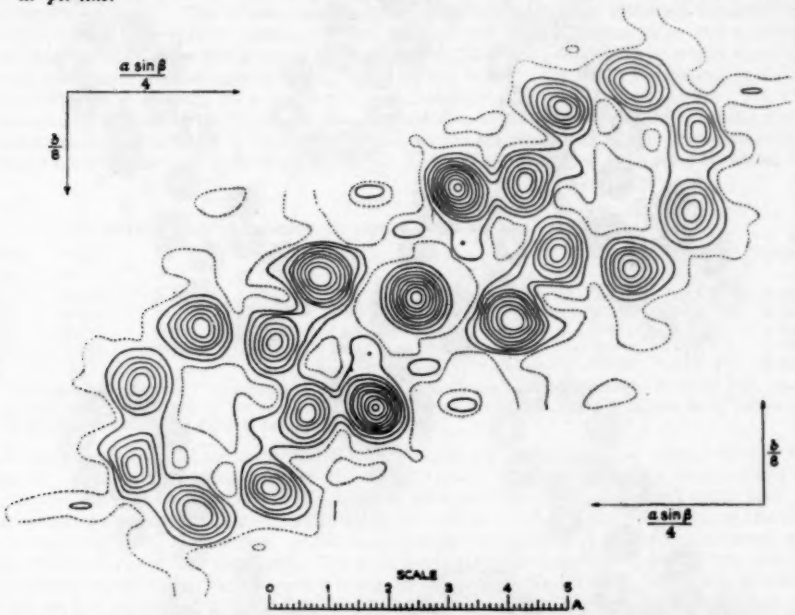
* As a very limited number of well-resolved peaks appear in the projection (Fig. 1), it would seem possible to arrive at the final solution without making use of any chemical information. Different selections of co-ordinates could be made from the pairs of peaks present, and the test of the right selection would be that which gave the best agreement in the structure factor calculations. This would be a possible although tedious process.

odd-index reflections, and so complete the synthesis. There is no difficulty in doing this because in each quadrant of the diagram there is found a ring of seven fairly low peaks which must be due to carbon atoms. Outside this ring and nearer to the central copper atom, there is a higher peak in each quadrant which must represent oxygen. The other oxygen atom and its mirror image coalesce to form an oval near the central copper, but an approximate co-ordinate can readily be assigned. The co-ordinates finally chosen are indicated by small black dots in the lower right-hand quadrant on Fig. 1.

These co-ordinates are listed in Table I, and were then used to calculate all the structure factors, with the results given in Table IV. The overall agreement obtained is quite good, the

FIG. 2.

Electron-density projection covering one molecule of cupric tropolone. Contour scale approximately one electron per A.^{2} *per line, the one-electron line being dotted. Scale on the copper atom, five electrons per* A.^{2} *per line.*



average discrepancy, obtained by dividing the sum of the individual discrepancies by the total of the measured F values, being only 15·8%. This confirms the selection of atoms taken as being correct. In these structure-factor calculations an averaged atomic *f*-curve for carbon and oxygen was used (Robertson, *Proc. Roy. Soc.*, 1935, *A*, **150**, 106), the atoms being weighted in the

TABLE I.

Co-ordinates derived from the first projection (*Fig.* 1).

Atom.	*x*/*a*.	*y*/*b*.	*X* (A.).	*Y* (A.).	Atom.	*x*/*a*.	*y*/*b*.	*X* (A.).	*Y* (A.).
Cu	0	0	0	0					
O(1)	0·139	−0·028	1·60	−0·38	CH(3)	0·209	0·230	2·40	3·17
O(2)	0·062	0·133	0·71	1·83	CH(4)	0·320	0·251	3·68	3·46
C(1)	0·202	0·050	2·32	0·69	CH(5)	0·410	0·202	4·72	2·78
C(2)	0·165	0·143	1·90	1·97	CH(6)	0·403	0·104	4·64	1·42
					CH(7)	0·315	0·035	3·62	0·48

ratio of 6 to 9. For copper an empirical scattering curve was used, of similar shape to the *f*-curve found for nickel in the nickel phthalocyanine structure (Robertson and Woodward, *J.*, 1937, 219). The measured F values were correlated with these calculated values, and so placed on at least an approximately absolute scale.

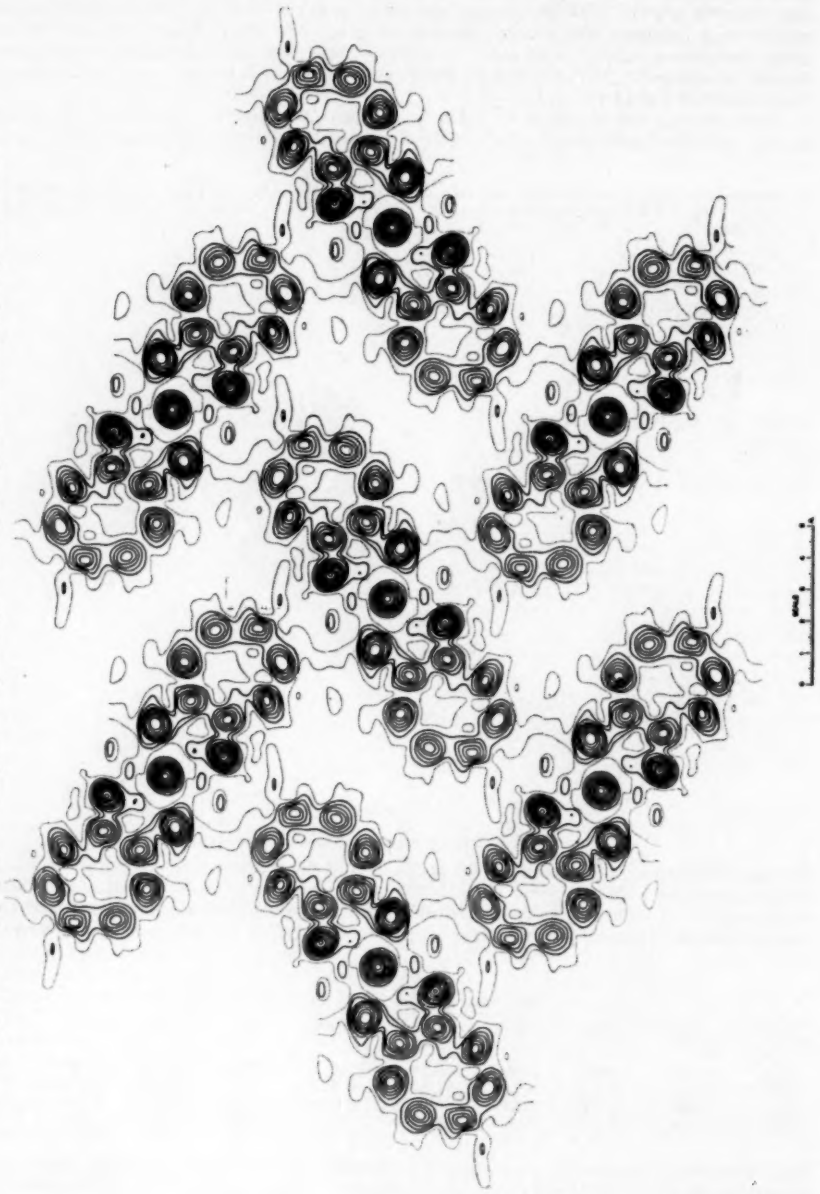


FIG. 3.

Electron-density projection showing the arrangement of several cupric tropolone molecules in the crystal structure.

It will be found that all the $(h + k)$-even structure factors still retain a positive sign in these calculations, which justifies our earlier assumption about the phase-determining power of the copper atom. As the signs of the $(h + k)$-odd structure factors are now known as well, we are in a position to proceed to a complete double Fourier synthesis, employing all the terms, which should give a faithful picture of the true structure.

The result of this calculation, extending over half the unit cell and covering one molecule of the complex, is shown in Fig. 2, and a smaller-scale drawing extending over several molecules is shown in Fig. 3. The Fourier summations were carried out by the 3-figure strip and stencil method (Robertson, *J. Sci. Instr.*, 1948, **25**, 28), the axial sub-divisions being $a/60 = 0{\cdot}193$ A. and $b/60 = 0{\cdot}230$ A., and the contour levels were plotted by graphical interpolation.

Interpretation and Discussion.

Examination of Fig. 2 will show that co-ordinates can now be assigned to all the atoms with considerable accuracy. The atoms are generally spherical in outline, although considerable distortions exist. No special significance can be attached to these distortions and spurious detail which are due in the first place to diffraction effects from the copper atom, where the peak value of the density is 47 as against 6 or 7 on the carbon atoms. (In Fig. 2 the contour scale on the central atom is reduced by a factor of 5 with respect to the rest of the diagram.) In the second place, the intensity estimates at present available are not very accurate. Taking these factors into account, however, it would appear that we can assign co-ordinates to the atoms which should be correct to within about 0·03 or 0·04 A. Table II gives a list of the values obtained.

Table II.

Co-ordinates and orientation (calculated from the final projection, Fig. 2).

Atom.	x/a.	y/b.	X (A.).	Y (A.).	Atom.	x/a.	y/b.	X (A.).	Y (A.).
Cu	0	0	0	0					
O(1)	0·137	−0·025	1·59	−0·35	CH(3)	0·209	0·229	2·42	3·17
O(2)	0·058	0·134	0·68	1·85	CH(4)	0·317	0·260	3·68	3·59
C(1)	0·203	0·054	2·36	0·75	CH(5)	0·408	0·201	4·73	2·78
C(2)	0·157	0·140	1·82	1·94	CH(6)	0·397	0·104	4·60	1·43
					CH(7)	0·310	0·036	3·59	0·49

Molecular orientation. The normal to the molecular plane makes an angle of 26·5° with the c crystal axis. The line in the molecular plane of zero inclination (perpendicular to c) makes an angle of 29° with the b crystal axis.

At the present stage of the analysis the third co-ordinate of the atoms (z) cannot be directly obtained. From a study of the outstanding features of the projection, however, a very probable assignment can be made from which it is possible to obtain the bond lengths and other data.

It is found that within narrow limits the seven carbon centres in the projection of the tropolone ring (Fig. 2) lie on an ellipse. After several trials with ellipses of different parameters, the result shown in Fig. 4 was obtained. The fit is quite accurate for most of the carbon centres, the deviation in the case of atoms 2 and 6 being not more than about 0·04 A. The circle of which this ellipse is a projection has a radius of 1·61 A., and there is a strong presumption that the atoms in the tropolone ring actually lie on this circle, for the following reasons. The ratio of the major to the minor axis of the ellipse is as 1·115 to 1, which corresponds accurately to the ratio of the length of the c crystal axis of cupric tropolone to the interplanar spacing of graphite (3·80 to 3·40). In all the phthalocyanine structures which have been examined by X-ray analysis, and in a large number of aromatic hydrocarbon structures, it is found that the perpendicular distance between overlying molecular planes is close to the graphite interplanar distance of 3·4 A. Indeed, this fact is often found to govern the crystal structure, and the length of the principal crystal axis depends only on this constant and the inclination of the molecular planes.

These various facts, and above all the regularity of the atomic arrangement in the tropolone ring, suggest very strongly that the carbon atoms must be almost exactly coplanar, and that the inclination of this plane to the c axis is $\cos^{-1}$ (minor axis of ellipse/major axis of ellipse) or $\cos^{-1}$ (3·40/3·80). For the angle of inclination, θ, this gives a value of 26·5°.

The fitting of the ellipse to the projection of the tropolone ring (Fig. 4) also gives the direction of inclination of the molecular plane, and so provides all the data required to calculate the interatomic distances. It is found that the major axis of the ellipse makes an angle of 29° with the b crystal axis. Lines in the projection parallel to this direction will have zero inclination, and perpendicular to this direction (the direction of the minor axis), they will have the maximum

inclination, θ (26·5°). In any other direction making an angle, α, with the direction of the minor axis, the angle ψ between a line in the molecular plane and its projection will be given by the relation

$$\tan \psi = \tan \theta \cos \alpha = 0{\cdot}499 \cos \alpha$$

and the true length, R, of a line whose measured length in the projection is r will be given by $R = r/\cos \psi$.

The interatomic distances given in Fig. 5 are calculated on this basis. It is assumed that the two oxygen atoms and the copper atom are coplanar with the tropolone ring. As the copper atom coincides with a centre of symmetry in the structure, it must be exactly coplanar with its four surrounding oxygen atoms. It is not necessary, however, that this plane should coincide with the plane of the tropolone ring. We make this assumption on the chemical evidence and also because it leads to a reasonable interpretation of the bond lengths.

The average value of the carbon–carbon bond length in the tropolone ring is 1·40 A. Deviations from this value are small, and it cannot be said with certainty that they exceed the possible error. The bond C(4)–C(5) at 1·45 A. is exceptionally long, and it is difficult to account for this value. It is not thought that much significance should be attached to this deviation because in this region the atoms are rather distorted and it is possible that the error here will be

FIG. 4.

Ellipse of major axis 1·61 A. *and minor axis* 1·44 A. *fitted to the carbon centres in the projection of the tropolone ring.*

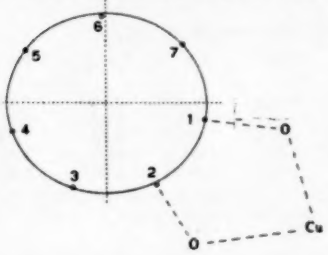
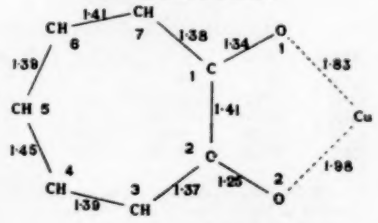


FIG. 5.

Interatomic distances.



greater than the average error. There is some evidence of a faint alternation of slightly longer and shorter bonds as we go round the ring, but the bond C(2)–C(3) might be expected to be of the longer type, like C(1)–C(2). This alternation, however, is so slight that very little significance can be attached to it at present. In general, it can be said that the resonance effect appears to stabilise the structure into an almost, if not quite, regular planar heptagon with average carbon–carbon bond length of 1·40 A.

Outside the tropolone ring, the bond-length measurements are capable of clearly differentiating the oxygen atoms. The distance of 1·34 A. between C(1) and O(1) corresponds to a hydroxylic link, whereas the distance of 1·25 A. from C(2) to O(2) corresponds to a carbonyl linkage. Further evidence that O(1) is indeed the hydroxylic oxygen is provided by the distance of 1·83 A. found between it and the copper atom, the other copper–oxygen distance being considerably greater at 1·98 A. In such circumstances the planar configuration of cupric copper with the formation of four covalent bonds of the dsp^2 type is to be expected, and recalls the structure of various compounds of copper with β-diketones (Cox and Webster, *J.*, 1935, 731).

The values found for the valency angles are collected with the bond-length measurements in Table III and do not call for much comment. The angles should be accurate to within about 3—4°. The theoretical angle for a regular heptagon is 128·6° and the angles found are all within

TABLE III.

Bond lengths and valency angles.

Cu–O(1) = 1·83 A.	C(3)–C(4) = 1·39	O(1)–Cu–O(2) = 84°	C(7)–C(1)–C(2) = 131°
Cu–O(2) = 1·98	C(4)–C(5) = 1·45	C(1)–O(1)–Cu = 112°	C(1)–C(2)–C(3) = 127°
C(2)–O(2) = 1·25	C(5)–C(6) = 1·39	C(2)–O(2)–Cu = 111°	C(2)–C(3)–C(4) = 131°
C(1)–O(1) = 1·34	C(6)–C(7) = 1·41	C(1)–C(2)–O(2) = 116°	C(3)–C(4)–C(5) = 129°
C(1)–C(2) = 1·41	C(7)–C(1) = 1·38	C(3)–C(2)–O(2) = 117°	C(4)–C(5)–C(6) = 125°
C(2)–C(3) = 1·37		C(2)–C(1)–O(1) = 118°	C(5)–C(6)–C(7) = 133°
		C(7)–C(1)–O(1) = 111°	C(6)–C(7)–C(1) = 126°

about 4° of this figure. The copper–oxygen bonds deviate somewhat from the expected square configuration, the angle being 84°.

Intermolecular distances have not been worked out in detail, but inspection of Fig. 3 makes it clear that they are all of the usual van der Waals type and are generally greater than 3·5 A.

TABLE IV.

Measured and calculated values of the structure factor.

hkl.	2 sin θ (λ = 1·542).	F, meas.	F, calc.	*hkl.*	2 sin θ (λ = 1·542).	F, meas.	F, calc.	*hkl.*	2 sin θ (λ = 1·542).	F, meas.	F, calc.
200	0·268	9	+14	410	0·547	5	+7	820	1·095	27	+30
400	0·536	<6	+12	420	0·581	25	+28	830	1·127	<6	−4
600	0·804	43	+39	430	0·632	<5	−4	840	1·165	26	+23
800	1·073	<6	+2	440	0·700	34	+36	850	1·211	21	+16
10,0,0	1·342	22	+25	460	0·860	19	+23	860	1·266	26	+23
12,0,0	1·609	11	+14	480	1·045	17	+20	880	1·400	13	+11
14,0,0	1·877	7	+7	490	1·142	15	−17	8,10,0	1·550	26	+22
				4,10,0	1·242	16	+16	8,12,0	1·720	14	+13
020	0·223	53	+51	4,11,0	1·341	<6	0	8,14,0	1·901	5	+9
040	0·447	65	+59	4,12,0	1·449	23	+18				
060	0·670	26	+30	4,14,0	1·660	13	+15	910	1·210	14	+15
080	0·894	54	+46	4,16,0	1·876	7	+13	920	1·228	14	+14
0,10,0	1·117	<7	+10					930	1·255	37	+31
0,12,0	1·341	<7	+5	510	0·683	40	+43	940	1·289	11	+6
0,14,0	1·564	<8	+8	520	0·710	18	−11	950	1·330	32	+25
0,16,0	1·788	8	+9	530	0·751	9	+16	960	1·381	16	+12
				540	0·810	<5	−3	970	1·439	<7	+6
110	0·174	74	+77	550	0·876	28	+30	990	1·570	6	+11
120	0·260	55	−54	560	0·950	7	−4	9,11,0	1·721	12	+12
130	0·360	44	+47	570	1·032	7	+10	9,13,0	1·901	7	+11
140	0·469	<6	+4	590	1·211	26	+26				
150	0·577	32	+36	5,11,0	1·401	13	+15	10,1,1	1·346	<7	−3
170	0·794	53	+53	5,13,0	1·607	21	+15	10,2,0	1·360	15	+13
190	1·016	29	+22					10,3,0	1·382	11	+9
1,11,0	1·239	<7	+7	610	0·813	25	−18	10,4,0	1·414	26	+22
1,12,0	1·350	11	+8	620	0·838	41	+40	10,10,0	1·745	13	+13
1,13,0	1·460	16	+18	630	0·873	11	−11	10,12,0	1·900	5	+10
1,15,0	1·689	13	+14	640	0·923	49	+45				
				650	0·981	4	−5	11,3,0	1·512	13	+13
210	0·289	13	+9	660	1·050	25	+26	11,4,0	1·542	<6	−5
220	0·348	39	+43	680	1·204	25	+24	11,5,0	1·579	5	+10
230	0·430	3	−4	6,10,0	1·375	<7	+4	11,6,0	1·621	6	−9
240	0·521	4	+3	6,12,0	1·569	19	+16	11,7,0	1·672	6	+13
250	0·620	37	+35					11,11,0	1·921	7	+11
260	0·723	37	+45	710	0·946	32	+32				
270	0·831	16	+9	720	0·965	<6	−6	12,1,0	1·613	14	+7
280	0·937	30	+28	730	0·999	37	+34	12,3,0	1·642	<6	0
290	1·045	<6	−3	740	1·042	5	−6	12,6,0	1·743	6	+12
2,10,0	1·152	37	+36	750	1·095	32	+30	12,8,0	1·841	9	+11
2,11,0	1·261	13	+13	770	1·223	26	+22	12,10,0	1·960	5	+11
2,12,0	1·372	17	+15	780	1·300	16	−14				
2,13,0	1·483	16	+13	790	1·379	15	+16	13,1,0	1·748	14	+11
2,14,0	1·595	15	+17	7,11,0	1·550	26	+19	13,3,0	1·777	6	+10
2,16,0	1·818	12	+12	7,13,0	1·734	<8	+7	13,5,0	1·830	5	+8
				7,15,0	1·927	5	+7	13,7,0	1·910	8	+13
310	0·416	24	+28								
320	0·460	35	−26					14,2,0	1·890	5	+7
330	0·526	37	+37					14,4,0	1·928	4	+6
340	0·602	21	+19					14,6,0	1·990	3	+8
350	0·690	22	+26								
360	0·782	35	+26								
370	0·883	30	+29								
380	0·983	14	+11								
390	1·088	23	+25								
3,11,0	1·297	26	+25								
3,13,0	1·514	6	+10								
3,15,0	1·731	15	+13								

It is a pleasure to express my thanks to Professor J. W. Cook and Dr. Raphael who supplied the crystals for this work, and to my two students, Mr. R. B. Campbell and Mr. G. Todd, for valuable assistance with part of the numerical work, and for a density determination.

CHEMISTRY DEPARTMENT,
THE UNIVERSITY, GLASGOW.

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274. *The Thermal Decomposition of Carbonyl Sulphide.*

By J. R. Partington and H. H. Neville.

The equilibrium conditions of the two decomposition reactions of carbonyl sulphide have been further investigated. The reaction leading to carbon dioxide is shown to be peculiarly susceptible to the nature of the vessel wall, and the rate of the reaction has been measured under various conditions. A method has been devised for measuring the rate of the fast reaction leading to carbon monoxide, and a number of velocity values have been obtained. The disproportionation of carbon monoxide, considered as a possible side reaction, is shown not to occur in the range of conditions studied.

The thermal decomposition of carbonyl sulphide (COS) into carbon monoxide and sulphur was described by Than (*Annalen*, 1867, Suppl. Vol. V, p. 236). Lewis and Lacey (*J. Amer. Chem. Soc.*, 1915, **37**, 1976) studied the equilibrium between carbonyl sulphide, carbon monoxide, and sulphur and attributed the 16% of the gas mixture unaccounted for by their analysis to two other reactions, $2COS = CO_2 + CS_2$ and $CS_2 = CS + S$. Meyer and Schuster (*Ber.*, 1911, **44**, 1931) passed carbon monoxide saturated with sulphur through a hot tube and observed the reaction $2CO + S_2 = CO_2 + CS_2$. On heating a mixture of carbon dioxide and carbon disulphide they detected the reverse reaction and stated that the further reaction $CO + S = COS$ occurred, though carbonyl sulphide was not specifically determined. They also showed that no sulphur dioxide was formed in these reactions, though Winternitz (Diss., Berlin, 1914, quoted by Stock and Seelig, *Ber.*, 1919, **52**, 681) stated that it could be produced by the reaction $4CO_2 + S_2 = 4CO + 2SO_2$. The rôle of carbonyl sulphide in these reactions was clarified by Stock and Seelig (*loc. cit.*), and Stock, Sieke, and Pohland (*Ber.*, 1924, **57**, 719), who showed that, when carbonyl sulphide was heated alone, two independent simultaneous equilibria arose: $2COS = CO_2 + CS_2$ ("CO_2 reaction") and $COS = CO + S$ ("CO reaction"), whilst interaction of any of the five substances in other combinations, and reactions leading to sulphur dioxide, carbon, or carbon monosulphide were negligible. Contrary to Lewis and Lacey, they found that the CO reaction was faster than the CO_2 reaction. The latter was catalysed by silica and the former proceeded to completion on a hot platinum wire. The CO equilibrium began to be measurable at 400°, while the CO_2 equilibrium was appreciable at room temperature. Klemenc (*Z. anorg. Chem.*, 1930, **191**, 246) found the CO_2 reaction entirely absent at 350°, except in one case in which the reaction vessel was filled with asbestos pellets. By calculating in terms of partial pressures some of the volumes of carbon dioxide and carbon disulphide found by Stock *et al.* (which are almost identical, as required by the CO_2 equation), Klemenc found the surprising result that the pressures of these two constituents were in the ratio 1 : 3, and so concluded that either the two equilibria could not exist simultaneously, or that they had shifted during Stock's analysis. This argument is evidently erroneous, as is seen by consideration of Klemenc's equation 2 (*loc. cit.*, p. 260).

We have further examined the variable nature of the CO_2 reaction and have shown that this is dependent on the nature and condition of the vessel wall. We have also measured the rates of both reactions under different conditions.

Experimental.

Carbonyl sulphide was prepared from Bender's salt (*Annalen*, 1868, **148**, 137) and dilute hydrochloric acid and was purified by passage through a bottle cooled to 0° to retain alcohol vapour, through 30% aqueous sodium hydroxide, concentrated sulphuric acid, through a trap at −55° to remove final traces of alcohol, and finally by condensation by liquid air. After evacuation, the carbonyl sulphide was distilled through a column of phosphoric oxide, head and tail fractions being rejected. The remainder was allowed to evaporate into the storage bulbs, head and tail fractions being again rejected. Six batches of about 4 l. each were prepared by this method.

Carbon dioxide from dilute sulphuric acid and sodium hydrogen carbonate was passed through two bubblers containing concentrated sulphuric acid and one trap at −70°, and condensed by liquid air. It was fractionated in the same way as the carbonyl sulphide.

Carbon monoxide from formic acid with concentrated sulphuric acid was passed through a liquid air trap and phosphoric oxide column.

Carbon disulphide from the AnalaR-quality product, shaken with mercury and redistilled, was stored in a small bulb attached to the apparatus only when required, owing to its effect on the tap-grease.

Oxygen from a cylinder was passed through a liquid-air trap and phosphoric oxide column.

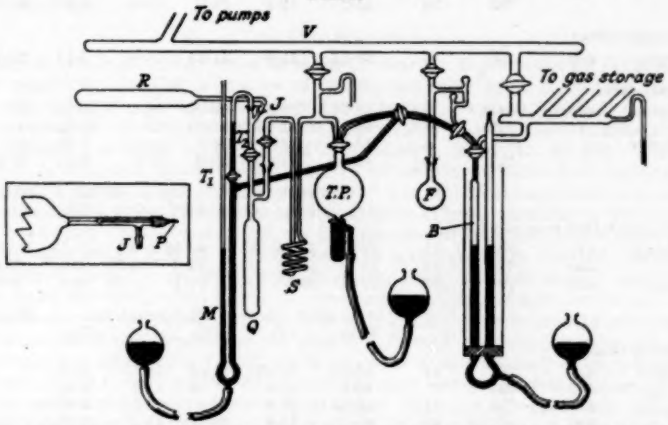
The apparatus is shown in Fig. 1. The main vacuum line V was connected to a mercury diffusion pump backed by a mechanical pump. The burette B served to measure out the gases used and to analyse the products. It was surrounded by a thermostat jacket at 30° ± 0·1° which also contained a levelling tube. The volume of gas could be read directly from the burette, and the pressure difference with a cathetometer.

Three reaction vessels were used, of "Pyrex," Jena glass, and silica. The first two were of the shape shown at R, and all three were provided with a similar connection at J. The "Pyrex" vessel was 27 × 3·1 cm., of volume 188·4 ml.; the Jena vessel was 22 × 3·9 cm., of volume 230·0 ml.

The silica vessel is shown inset below R in Fig. 1 (on a larger scale). It was designed to overcome the difficulty in the CO reaction due to condensation of sulphur on cold parts of the apparatus. The capillary tube from the body of the vessel was sealed by a silica plunger P with a point ground to fit the expanded end of the capillary, into which it could be tightly pressed by the tension of a piece of thick rubber tubing. The joint J connected with the rest of the apparatus, and gas could enter or leave the vessel through J and the annular space round the plunger when the latter was withdrawn a few mm. (to the right). The capillary connection and plunger valve were just outside the furnace and were kept at about 460° by a small auxiliary furnace. This valve, though not gas tight, was able to prevent diffusion of sulphur vapour into the cold parts during the short runs. Actual loss of gas was prevented by tap T_2. The volume of the vessel was 505·1 ml. and the dead space outside the valve was 2·2 ml.

Communicating with the reaction vessel was a manometer M with a levelling device whereby the mercury in the limb communicating with R could be adjusted to the same height at all pressures. In

FIG. 1.



this limb was a tap T_1 and a side-arm leading *via* capillary tubing to the burette. The normal method of introducing gas into R was to measure it out in B and, after lowering the mercury in M below the side-arm, to drive the gas over completely from B, the capillary connections remaining filled with mercury at the end.

At the end of a run the gas mixture was withdrawn from R by cooling the evacuated quenching vessel Q in liquid air and quickly opening T_2. Any uncondensed gas was drawn off by the Töpler pump TP, transferred to the burette, measured, and rejected. By closing T_2 and surrounding Q with suitable cooling baths, fractions of the condensate in Q could similarly be pumped off and measured, the gas in all cases having to pass through the spiral S. Gas to be determined after absorption in a liquid reagent could be transferred from B to the flask F, subsequently detached for analysis of the resulting solution.

The reaction vessels were heated in a tubular electric furnace, 40 cm. × 8 cm. bore, being the inside of a steel tube 6 mm. thick. Temperature was measured with a platinum/platinum–rhodium thermocouple with its cold junction in ice, and a galvanometer calibrated against a potentiometer. Temperatures are given to the nearest 5°. The furnace was closed with a plug at the left-hand end, and with a slotted shield at the other. The joint J was sealed with picein wax, and at higher furnace temperatures wound over with asbestos string kept wet.

Analysis of Reaction Products.—The course of the reaction was followed by analysis since the CO_2 reaction gives no pressure change and the CO reaction is too fast to make pressure readings practicable. The resulting reaction mixture might contain carbonyl sulphide, carbon dioxide, carbon disulphide, carbon monoxide, and sulphur. On quenching in liquid air carbon monoxide alone remained and could be measured as described. Sulphur was not determined. By surrounding the condensate with a bath at −100° to −110°, carbonyl sulphide and carbon dioxide together could be pumped off and measured, leaving the carbon disulphide in Q. The spiral S was always at the same temperature as

TABLE I.

Run.	Vessel.	Temp.	Press., mm.	Time, hrs.	Gas used, ml. COS.	Gas used, ml. CO.	Gas found, ml. COS.	Gas found, ml. CO.	Gas found, ml. CO_2.	Reaction, %. "CO_2."	Reaction, %. "CO."
Suppression of CO reaction.											
7	Pyrex	460°	748	17	72·7	—	54·5	4·0	7·55	22	7
10	,,	455	686	41	70·0	16·3	46·45	16·45	11·55	33	0
Time to reach CO_2 equilibrium at 450°.											
12	Pyrex	445	774	4	59·4	16·65	58·0	16·65	0·7	2·5	—
11	,,	455	805	18	62·2	16·55	53·2	16·7	4·5	23	—
13	,,	460	820	20	64·75	17·2	47·95	17·2	8·45	26	—
14	,,	440	825	39½	64·5	17·35	48·6	17·3	8·25	25	—
22	,,	450	800	68½	58·4	16·95	14·4	16·15	8·95	29	—
With silica filling.											
26	Pyrex	450	712	4	39·4	13·15	25·65	13·4	7·25	36	—
24	,,	,,	718	17	40·15	13·2	25·35	13·35	7·55	37	—
25	,,	,,	723	24	40·35	13·4	25·05	13·75	7·15	36	—
With Pyrex filling.											
27	Pyrex	450	712	4	40·2	13·15	29·05	13·1	5·55	27	—
28	,,	,,	700	18	39·6	13·05	27·5	12·85	6·1	30·5	—
35	,,	,,	735	70	41·2	13·8	29·0	13·9	6·2	30	—
With small silica filling.											
72	Pyrex	450	750	3	60·15	15·9	41·05	15·8	9·85	32·5	—
Effect of vessel wall.											
19	Jena	450	849	4	81·45	25·85	56·05	26·1	13·25	33	—
29	,,	,,	756	4	69·45	21·55	47·25	21·45	11·05	32	—
32	Pyrex	,,	771	4	42·05	14·3	31·2	14·45	5·35	28	—
33	,,	,,	754	25½	41·15	14·85	33·0	15·0	4·2	20·5	—

Run.	Vessel.	Temp.	Press., mm.	Time, hrs.	Gas used, ml. CO.	Gas used, ml. CO_2.	Gas used, ml. CS_2.	Gas found, ml. COS.	Gas found, ml. CO.	Gas found, ml. CO_2.	Reaction, %. CS_2.	Reaction, %. "CO_2."
Equilibrium approached from reverse side.												
37	Pyrex	475	725	13	22·65	37·75	32·75	45·95	22·7	15·65	9·75	37
38	,,	450	718	24	13·35	19·05	19·05	29·3	13·35	6·5	4·4	27
39	Jena	455	706	16	13·65	20·55	19·8	27·4	13·65	6·9	6·05	32

Run.	Vessel.	Temp.	Press., mm.	Time, hrs.	Gas used, ml. COS.	Gas used, ml. CO.	Gas found, ml. COS.	Gas found, ml. CO.	Gas found, ml. CO_2.	Reaction, %. "CO_2."
Oxygen cleaning method.										
41	Pyrex	445	707	44	40·05	13·05	31·05	13·25	4·65	23
42	,,	445	734	41	40·6	13·0	27·55	13·2	6·55	32
43	,,	465	730	51	40·85	13·3	32·5	13·35	4·3	21
44	,,	450	711	42	40·7	13·4	28·15	13·3	6·25	31
With excess inert gas; "Pyrex," series (a).										
53	Pyrex	450	540	7½	39·25	11·0	28·95	10·85	5·2	26
53a	,,	,,	540	,,	39·55	11·35	29·65	11·1	5·0	25
52	,,	,,	380	,,	26·5	8·3	22·55	8·05	2·0	15
54	,,	,,	315	,,	22·35	5·6	19·5	5·7	1·35	12
55	,,	,,	175	,,	12·1	4·1	11·4	4·05	0·35	6
With excess inert gas; "Pyrex," series (b).										
51	Pyrex	450	805	7½	29·3	46·65	24·3	46·4	2·55	17
58	,,	,,	774	,,	17·9	54·5	15·65	54·6	1·1	12
71	,,	,,	705	,,	13·55	58·7	11·75	59·15	0·8	12
With excess inert gas, silica, series (a).										
70	Pyrex	450	460	2	37·25	10·55	26·0	10·45	5·65	30
67	,,	,,	280	,,	22·35	6·65	16·6	6·85	2·95	26·5
64	,,	,,	184	,,	14·15	5·15	11·2	4·95	1·45	23
68	,,	,,	113	,,	8·6	3·75	7·25	3·6	0·65	15
With excess inert gas; silica, series (b).										
69	Pyrex	450	815	2	38·35	47·15	28·15	47·9	5·35	28
66	,,	,,	860	,,	24·85	64·75	20·45	64·8	2·15	17
65	,,	,,	880	,,	14·15	78·6	13·2	79·15	0·55	8

A few exploratory runs with CO and CO_2 reactions have been omitted.

TABLE I—*continued.*

Run.	Vessel.	Temp.	Press., mm.	Time, hrs.	Gas used, ml. COS.	Gas used, ml. CO.	Gas found, ml. COS.	Gas found, ml. CO.	Gas found, ml. CO_2.	Reaction, %. "CO_2."
Velocity coefficient, additional runs.										
74	Jena	450	452	50 min.	37·8	10·4	29·25	10·55	4·15	22
86	,,	325	330	22 hrs.	41·7	—	37·7	0·0	2·15	10·5
87	,,	,,	369	74	45·55	—	29·85	0·0	7·75	34
109	,,	400	490	4	45·8	8·5	34·6	8·5	5·65	24
108	,,	,,	495	54	44·85	10·45	28·3	10·35	8·25	37

Q, so as to retain traces of vapour which might be carried over. This was essential when pumping off carbon monoxide, which otherwise contained measurable amounts of carbonyl sulphide or carbon dioxide. The composition of the mixture of carbonyl sulphide and carbon dioxide was found by absorption in 10% aqueous potassium hydroxide, followed by conversion of sulphide into sulphate with bromine, and determination as barium sulphate. Two hours' contact of gas with solution was found to be sufficient. Various methods of determining the residue of carbon disulphide were tried without success, chiefly owing to retention of carbon disulphide by tap-grease and by sulphur formed in the reaction. Since carbon disulphide is produced in equimolecular amount with carbon dioxide, the separate determination of carbon disulphide was not necessary (cf. Stock, Sieke, and Pohland, *loc. cit.*) and the amount of carbon disulphide was assumed to equal that of the carbon dioxide.

Table I gives the results of the experiments. The gas volumes are in ml. at S.T.P., and the amount of reaction calculated as: CO_2 reaction $= 100(CO_2 + CS_2)/(COS + CO_2 + CS_2)$, and CO reaction $= 100CO/(COS + CO)$.

THE CO_2 REACTION.

The CO_2 reaction is more easily studied if the CO reaction is prevented by the prior addition of carbon monoxide. At 450° a volume of carbon monoxide equal to 25% of the carbonyl sulphide used makes the CO reaction undetectable, as runs 7 and 10 (Table I) show.

The time taken to reach equilibrium in the CO_2 reaction at 450° was determined by making 5 runs of increasing duration in the " Pyrex " vessel (nos. 12, 11, 13, 14, 22). These showed an approach to maximum decomposition after 70 hours, but the individual points did not lie on a well-defined curve. Stock, Sieke, and Pohland (*loc. cit.*) found equilibrium at about 40% decomposition after 4 hours; hence our conditions were different, possibly in the nature of the surface of the vessel. Stock *et al.* found the CO_2 reaction to be catalysed by silica, which was confirmed by runs 26, 24, and 25, in which results in agreement with those of Stock *et al.* were found with the " Pyrex " vessel filled with silica chips (80 g.; 10—20 mesh; boiled with aqua regia), the vessel and filling being heated in a vacuum for 2 hours at 450° before use.

The discrepancy in the results with the unfilled " Pyrex " vessel was evidently due to some specific surface influence. Increasing the area of " Pyrex " produced some acceleration, but not as much as the silica (runs 27 and 28, in which 80 g. of " Pyrex " chips, prepared in the same way as the silica, were used). Even with 70 hours' contact with the increased " Pyrex " surface, the maximum decomposition was no nearer the value obtained with silica (run 35). The greater catalytic power of silica appears in run 72 in which 4 g. of silica chips produced, in a shorter time, a greater decomposition than the full " Pyrex " filling.

A few runs (*e.g.*, nos. 19, 29) showed that the Jena glass vessel was almost as effective as the silica, the decomposition being over 30% in 4 hours. Run 29 was carried out some time after run 19; immediately following run 19 some similar runs with the Jena vessel produced hardly any decomposition (about 1%). Freshly prepared carbonyl sulphide and carbon monoxide gave the same result. Two runs with the " Pyrex " vessel with " Pyrex" filling (nos. 32, 33) were then made under otherwise similar conditions; the first was successful (cf. no. 27), and the second gave less decomposition in a longer time.

It was evident that contamination of the surface was inhibiting the reaction, this effect being much more marked with " Pyrex " than with silica. Approach towards equilibrium from the reverse direction gave a similar result; run 37 (silica filling) giving an equilibrium corresponding to 37% decomposition, run 38 (" Pyrex " filling) 27%, and run 39 (Jena vessel) 32%. (In these reverse runs the carbon disulphide was calculated as the remainder of the initial carbon disulphide after deduction of the volume converted into carbonyl sulphide, instead of being put equal to the carbon dioxide.)

Boiling the vessels and fillings with aqua regia, washing with much distilled water, and baking out at 450° under vacuum restored the activity to some extent, but heating in contact with oxygen was more effective, as is shown by runs 41—44 in which the vessel with " Pyrex " filling was alternately not cleaned and cleaned by heating at 450—500° with oxygen for 4—5 hours at 1 atmosphere. The oxygen cleaning technique was used in all subsequent runs.

Evidently the CO_2 reaction is catalysed by silica. With " Pyrex " an increase of surface area accelerated the reaction, but not to the same extent, and with the minimum " Pyrex " surface the reaction was very slow. In the unpacked " Pyrex " vessel, there might, therefore, be a proportion of homogeneous reaction. This was examined by allowing the reaction to proceed in presence of an inert gas in contact with each surface in turn. Carbon monoxide as " inert " gas was added in excess of the amount required to suppress the CO reaction. The rate of reaction was determined with the unfilled " Pyrex " vessel and with the Jena vessel with silica filling (*a*) with various partial pressures of carbonyl sulphide and the normal amount (25%) of carbon monoxide added, and (*b*) with various partial pressures of carbonyl sulphide and increasing amounts of carbon monoxide to maintain the total pressure at about 1 atmosphere. For comparison the rate of reaction was taken as the per cent. CO_2 reaction in 7½ hours (" Pyrex ") or 2 hours (silica). The two series of runs with each surface are given in Table I and are shown graphically in Fig. 2 (" Pyrex ") and Fig. 3 (silica). The open circles

FIG. 2.

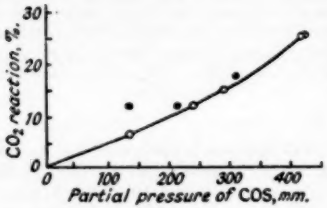
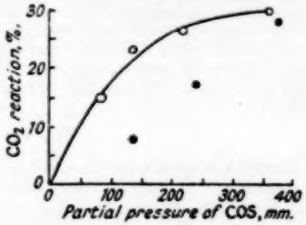


FIG. 3.



represent runs with the normal amount of carbon monoxide, and the full circles with excess of carbon monoxide.

Before consideration of these results, the velocity coefficient of the CO_2 reaction may be mentioned. The bimolecular coefficient for the reaction $2COS \rightleftharpoons CO_2 + CS_2$ was calculated for the reaction in " Pyrex " and in presence of silica from the two series (*a*) of the previous section, in which the normal amount of carbon monoxide was added, together with the additional runs shown at the end of Table I, with the Jena vessel with silica filling, at different temperatures and of different duration. Runs 87 and 108 give the equilibria at 325° and 400° with 34% and 37% CO_2 reaction respectively, in agreement with Stock, Sieke, and Pohland's values (*loc. cit.*). The bimolecular velocity coefficients are given in Table II.

The activation energies for the silica surface are 28,160 cals. between 325° and 400°, and 28,570 cals. between 400° and 450°, the mean being 28,450 cals.

TABLE II.

Silica surface.			" Pyrex " surface.		
Temp.	Run.	10^3k.	Temp.	Run.	10^3k.
450°	70	9·2	450°	53	1·81
	67	11·6		53a	1·65
	64	13·8		52	1·16
	68	13·0		54	0·61
	74	11·8		55	0·82
	Mean	11·9		Mean	1·20
400°	109	2·36			
325°	86	0·167			

The runs with the silica surface show that a second-order heterogeneous reaction takes place with a well-defined rate, but an interpretation of the results with " Pyrex " and Jena glass is not so easy. The CO_2 reaction rate has not previously been measured, but it is clear that its occurrence in the absence of silica is variable. It undoubtedly occurred in the work of Stock *et al.* with Jena glass, and of Lewis and Lacey with glass, but Russell (*J.*, 1900, **77**, 361) and Klemenc (*loc. cit.*) found it absent in vessels of glass and Jena glass, respectively. Gilfillan (*J Amer. Chem. Soc.*, 1922, **44**, 1329) passed carbon dioxide with carbon disulphide through a silica tube containing pumice at 400°, no carbonyl sulphide being found in the issuing gas. In the present work the reaction was found to occur and not to occur with the same surface, " Pyrex " or Jena, and the condition of the surface is responsible for this variation.

A reaction in the gas phase, if possible, would be expected to be slower than the catalysed reaction. The results with " Pyrex " indicated a much slower reaction, but since consistent results were not found with this surface, it is probable that they do not relate to a pure uncomplicated homogeneous reaction. The occurrence or non-occurrence of the reaction, or its variable extent according to the condition of the surface, seems to negative a homogeneous reaction, but the experiments with excess of inert gas (Fig. 2) offer an explanation. Since addition of inert gas does not retard it, it seems that the reaction can proceed without contact with the surface. That the inert-gas technique is effective in this particular experimental arrangement is clearly demonstrated by the runs with silica (Fig. 3) which show that the reaction is, in fact, distinctly slower in presence of inert gas. At the lowest pressures with the " Pyrex " surface, however, there is an indication of acceleration of the reaction with increasing proportion of inert gas, which suggests that the surface effect enhances a subsidiary reaction re-forming carbonyl sulphide, or producing some substance emitted into the gas phase and able to inhibit homogeneous decomposition; this effect predominates when the surface is not treated with aqua regia, oxygen, etc.

In many runs at 450° a very faint dark mirror-like deposit formed in the outlet tube of the reaction vessel, too small for detailed examination but burning off in oxygen at about the same temperature as a comparison film of carbon, and not volatilised at the softening point of " Pyrex " in the absence of oxygen. This deposit was probably carbon from traces of organic impurity, and it is possible that an even thinner deposit on the main part of the vessel was responsible for the observed surface effects.

The Reaction $2CO \rightleftharpoons CO_2 + C$.

Stock *et al.* showed that of the possible side reactions in the decomposition of carbonyl sulphide only the decomposition of carbon monoxide was significant, and allowance was made for this. The available information on this reaction is somewhat uncertain. Deville (*Compt. rend.*, 1864, **59**, 373) stated that carbon monoxide is reversibly decomposed at a bright-red heat, and Berthelot (*Ann. Chim. Phys.*, 1879, **17**, 129) that the proportion decomposed was only a few thousandths. The equilibrium was examined by Boudouard (*ibid.*, 1901, **24**, 5) and by Fester and Brude (*Ber.*, 1923, **56**, 2245) in presence of catalysts down to lower temperatures, and Rhead and Wheeler studied the effect of temperature (*J.*, 1910, **97**, 2178) and pressure (*J.*, 1911, **99**, 1140). The reaction is exothermic and the formation of carbon dioxide is favoured at low temperatures. All these authors passed carbon monoxide over heated carbon, sometimes with addition of pumice, silica, etc., and in our experiments carbon was not initially present. Stock, Sieke, and Pohland (*loc. cit.*) with carbon monoxide alone found only slight decomposition subject to unpredictable catalytic influences, or none at all. A trace of water vapour and an increase of surface enhanced the decomposition. Cleminson and Briscoe (*J.*, 1926, 2148) found no appreciable reaction at 300° in clean glass vessels.

It was, therefore, difficult to assess the importance of this reaction and we examined it in our own apparatus under conditions similar to those used with carbonyl sulphide. A quantity of carbon monoxide was heated and the products quenched. The volume of gas (*a*) condensed in liquid air, (*b*) uncondensed in liquid air was measured. Four runs are given in Table III.

Table III.

					Gas used, ml.		Gas found, ml.	
Run.	Vessel.	Temp.	Press., mm.	Time.	CO.	CO_2.	CO.	CO_2.
60	Pyrex	550°	360	5 hrs.	30·15	—	30·1	0·0
62	,,	500	717	21 ,,	66·65	—	66·55	0·5
78	Silica	650	562	20 min.	123·2	—	123·05	0·3
81	,,	645	345	30 ,,	45·85	26·0	45·8	26·15

In the first three runs a negligible amount of carbon monoxide decomposed, in the fourth a mixture of carbon monoxide and dioxide remained unchanged under conditions corresponding to those of the CO decomposition of carbonyl sulphide. It was concluded that under these conditions decomposition of carbon monoxide, or reaction between carbon monoxide and dioxide, would not interfere with the main reaction.

The CO Reaction.

Preliminary experiments showed that in short runs the CO_2 reaction was absent or negligible and could be repressed by prior addition of carbon dioxide. In the analyses, therefore, only the carbon monoxide formed from a known volume of carbonyl sulphide need be determined.

In short runs it was important to introduce the carbonyl sulphide as quickly as possible. Carbon dioxide, when added, was introduced first. As much as 90 ml. of carbonyl sulphide could be introduced in 4—5 seconds. Withdrawal of products was effected by holding open the plunger valve and the tap leading to the evacuated and cooled quenching vessel for 1 minute. Trials with carbon dioxide alone showed that all but about 1 ml. of gas was withdrawn within 5 seconds. The duration of a run was measured from 2 seconds after the beginning of admission of carbonyl sulphide to 2 seconds after beginning of withdrawal. The pressure in the reaction vessel was calculated from the volumes of gases used, the extent of decomposition and the temperature. The equilibrium was determined at 4 temperatures between 500° and 650°. Run 82 (Table IV), for example, shows 28% CO reaction at 650° after 10 minutes, and runs of twice the duration with twice the amount of added carbon dioxide gave no greater decomposition.

TABLE IV.

(All runs in the silica vessel.)

Run.	Temp.	Press., atm.	Time, min.	Gas used, ml. CO_2.	Gas used, ml. COS.	Found, ml. CO.	Reaction, %. CO.
Determination of equilibrium.							
82	650°	0·779	10	19·95	86·9	19·1	22
104	600	0·814	15	35·25	88·45	10·25	11·5
91	550	0·653	15	19·4	88·45	7·65	9
90	500	0·608	15	21·05	92·4	5·05	5·5
Velocity coefficient.							
96	600	0·592	0·75	—	89·75	7·85	9
99	,,	0·247	,,	—	37·4	1·95	5·5
101	,,	0·384	,,	—	58·85	4·2	7
89	550	0·546	5	—	89·5	5·25	5·5
93	,,	0·539	6·43	—	56·8	6·15	7
105	,,	0·810	6	—	131·45	8·6	6·5
With excess of CO_2 added.							
98	600	0·918	0·75	50·75	90·65	7·5	8
103	,,	0·795	,,	65·15	58·55	3·9	6·5
With 100 g. of silica chips.							
106	550	0·669	5	—	98·25	8·75	9
107	,,	0·505	2	—	74·8	4·95	6·5

The equilibrium constants from the first set of runs are compared in Table V with those of Stock *et al.*, which were obtained by calculation from experiments at 800° and 950° (in which the CO_2 reaction was not repressed, but allowed for by extrapolation of data obtained for this reaction up to 450°).

TABLE V.

Temp.	Decomposed, % (corr. to 1 atm.).	10^3K_p.	Decomposed, % (Stock, 1 atm.).	10^3K_p (Stock).
650°	19	4·7	15	2·34
600	10	0·77	9	0·49
550	8	0·275	5	0·255
500	4·5	0·055	2·5	0·0099

The rate of the reaction was measured in the rather narrow temperature range 550—600°; above 600° it was too fast to measure and below 550° the equilibrium was unfavourable. Three runs with different concentrations made at each temperature without addition of carbon dioxide are given in the second section of Table IV. Three possible reactions may be considered: (*a*) $COS \rightleftharpoons CO + S$, (*b*) $2COS \rightleftharpoons 2CO + S_2$, (*c*) $COS = CO + S$ together with $2CO + S_2 = 2COS$. Case (*b*) was evaluated by the method used by Bodenstein and Krauss (*Z. physikal. Chem.*, 1936, **175**, *A*, 295). The reverse reaction appears to be negligible, and case (*c*) is similar, so that the velocity coefficients obtained represent respectively a unimolecular forward with bimolecular reverse reaction, a bimolecular irreversible reaction, and a unimolecular irreversible reaction. Table VI shows the velocity coefficients for each case.

The mean value of k in each case gives an activation energy (*a*) 58,900, (*b*) 74,400, (*c*) 72,800 cals.

Addition of carbon dioxide as inert gas (runs 98, 103; Table IV) produced little diminution in velocity, these runs being otherwise comparable with nos. 96 and 101, respectively, in which no carbon dioxide was added. Two runs with silica filling (nos. 106, 107) resulted in 9% reaction after 5 minutes and 6·5% after 2 minutes. The equilibrium decomposition at the

TABLE VI.

		10^3k.					10^3k.		
Run.	Temp.	(*a*).	(*b*).	(*c*).	Run.	Temp.	(*a*).	(*b*).	(*c*).
93	550°	0·251	13·8	0·203	99	600°	1·31	196	1·26
89	,,	0·215	12·3	0·189	101	,,	1·74	161	3·62
105	,,	0·241	10·3	0·147	96	,,	2·55	138	2·10

temperature of these runs is 8% at 1 atmosphere, or 9% at the pressure of run 106, so in this run equilibrium was reached in less than 5 minutes, whilst in the unpacked vessel only 5·5% decomposition occurred in the same time (run 89). In run 107 equilibrium had not been reached in 2 minutes, so the effect of the silica filling is not very marked.

The CO reaction seems more straightforward than the CO_2 reaction, but can be studied only in a small temperature range, so that it was not possible to achieve certainty on the orders of the forward and reverse reactions by rate measurements. The reaction is not markedly heterogeneous in contact with silica, perhaps partly because in the short time there was incomplete access of the gas to the surface.

In conclusion we acknowledge the receipt of grants for the purchase of apparatus from the Chemical Society Research Fund, and from the Central Research Fund of London University.

QUEEN MARY COLLEGE (UNIVERSITY OF LONDON). [*Received, December* 15th, 1950.]

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275. *Naturally Occurring Quinones. A New Synthesis of Plumbagin and a Note on the Structure of* β*-Hydroplumbagin.*

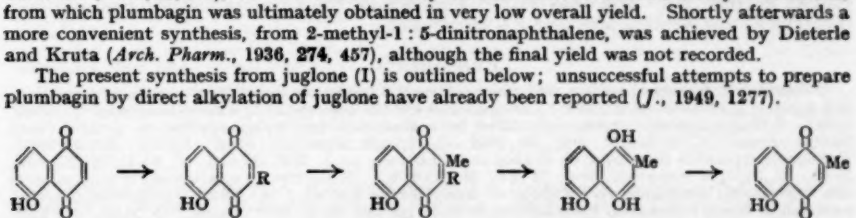
By R. H. THOMSON.

Plumbagin (IV) has been synthesised from 3-carboxymethylthio-2-methyljuglone (II; R = S·CH_2·CO_2H) by hydrogenolysis with Raney nickel followed by oxidation. β-Hydroplumbagin is shown to be 2 : 3-dihydro-5-hydroxy-2-methyl-1 : 4-naphthaquinone (VI).

To complete earlier work (*J.*, 1950, 1737) on the structure of β-hydrojuglone and other known compounds of the series, plumbagin has now been synthesised and converted into β-hydroplumbagin.

Plumbagin (IV) occurs in various *Plumbago* and *Drosera* species but is not readily available from natural sources in this country. It was first obtained synthetically by Saenz de Buruaga and Verdú (*Anal. Fís. Quím.*, 1934, **32**, 830) by oxidation of 2-methyl-1 : 4-naphthaquinone with Caro's acid, but the product was mixed with much unchanged starting material and an unidentified compound. The structure (IV) was established by Fieser and Dunn (*J. Amer. Chem. Soc.*, 1936, **58**, 572), who converted *m*-toluoyl chloride into the desired 6-methyl-1-tetralone, from which plumbagin was ultimately obtained in very low overall yield. Shortly afterwards a more convenient synthesis, from 2-methyl-1 : 5-dinitronaphthalene, was achieved by Dieterle and Kruta (*Arch. Pharm.*, 1936, **274**, 457), although the final yield was not recorded.

The present synthesis from juglone (I) is outlined below; unsuccessful attempts to prepare plumbagin by direct alkylation of juglone have already been reported (*J.*, 1949, 1277).

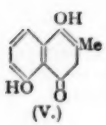


Initially, efforts were made to debrominate 3-bromo-2-methyljuglone (II; R = Br) by reduction with hydrogen and a palladium–barium sulphate catalyst in glacial acetic acid in the presence of sodium acetate, followed by immediate oxidation of the α-hydroplumbagin (III) so

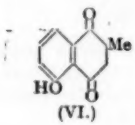
obtained. This was not successful, although trial experiments with 3-bromojuglone yielded small amounts of bromine-free quinone. The acetate of (II; R = Br) and the corresponding triacetate obtained by reductive acetylation were also tried, but only traces of the appropriate plumbagin derivatives were isolated.

Attention was then turned to thio-ether derivatives. Addition of thiols to juglone yields 3-substituted derivatives, but the corresponding plumbagin derivatives were prepared preferably from 3-chloro-2-methyljuglone. Model experiments showed that hydrogenolysis of 3-alkyl- and -aryl-thiojuglones with Raney nickel and subsequent oxidation to juglone was feasible, although yields were poor. However no plumbagin was obtained from 2-methyl-3-*p*-tolylthiojuglone (II; R = *p*-Me·C_6H_4·S) by this method, and 1 : 4 : 5-triacetoxy-2-methyl-3-*p*-tolylthionaphthalene yielded only trifling amounts of α-hydroplumbagin triacetate. The difficulty appeared to arise in the oxidation stage, and to avoid this the solution of α-hydroplumbagin obtained by hydrogenolysis was boiled with acid stannous chloride solution to convert the α- into the more stable β-isomer (cf. α- and β-hydrojuglones, *J.*, 1950, 1737). With 3-ethylthio-2-methyljuglone (II; R = EtS) this procedure yielded at first a new yellow compound, m. p. 164°. Similarly, an attempt to obtain β-hydrojuglone from 3-ethylthiojuglone afforded another new yellow substance, m. p. 181°. These compounds (which are at present under investigation) contain more hydrogen than would the expected hydroquinones, and by reduction of the reaction time and the amount of Raney nickel, their formation was largely avoided (the hydroquinones are not reduced by boiling acid stannous chloride solution). The isolation of β-hydroplumbagin at this stage was not pursued. Plumbagin was finally obtained by hydrogenolysis of 3-carboxymethylthio-2-methyljuglone (II; R = S·CH_2·CO_2H), the resulting α-hydroplumbagin being transferred to acid stannous chloride solution, and, after removal of the yellow compound, oxidised with hydrogen peroxide.

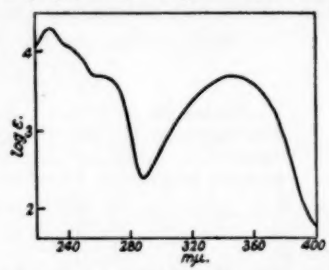
β-Hydroplumbagin was prepared by fusion of the α-isomer. As the compound formed only a monophenylsemicarbazone, Olay (*Rev. Acad. cienc. Madrid*, 1935, **32**, 384) tentatively proposed the monoketo-structure (V). Although all attempts to prepare dicarbonyl derivatives have



(V.)



(VI.)



failed, no enolic group at $C_{(1)}$ could be detected. The compound dissolves slowly in cold dilute alkali regenerating the α-isomer, but Zerewitinoff estimation indicated only one active hydrogen atom. Spectroscopic examination of β-hydroplumbagin showed clearly that it has the structure (VI). The infra-red spectra of both a crystalline sample and a dilute carbon tetrachloride solution show no free hydroxyl band in the 3600-cm.$^{-1}$ region whereas two carbonyl bands are present at 1695 cm.$^{-1}$ and 1645 cm.$^{-1}$. Furthermore the ultra-violet absorption spectrum (figure) is almost identical with that of β-hydrojuglone.

Experimental.

3-Bromo-2-methyljuglone.—This was prepared from 3-bromojuglone (4·38 g.) and acetyl peroxide (2·3 g.) in glacial acetic acid (36 c.c.) as described for the corresponding chloro-compound (*J.*, 1949, 1278). 3-Bromo-2-methyljuglone crystallised from alcohol in fine orange needles, m. p. 118° (yield 18·5%) (Found: C, 49·35; H, 2·8; Br, 29·6. $C_{11}H_7O_3Br$ requires C, 49·45; H, 2·6; Br, 29·95%). The *acetate* separated from aqueous alcohol in yellow rods, m. p. 152° (Found: C, 50·1; H, 2·8; Br, 25·65. $C_{13}H_9O_4Br$ requires C, 50·5; H, 2·9; Br, 25·85%). Reductive acetylation of the quinone with zinc dust, acetic anhydride, and 2 drops of triethylamine yielded 1 : 4 : 5-*triacetoxy-3-bromo-2-methylnaphthalene* which crystallised from alcohol in short needles, m. p. 191° (Found: C, 51·65; H, 3·55; Br, 20·1. $C_{17}H_{15}O_6Br$ requires C, 51·65; H, 3·8; Br, 20·2%).

3-Phenylthiojuglone.—(*a*) Juglone (0·87 g.) was dissolved in warm alcohol (40 c.c.), the solution cooled quickly to room temperature, and benzenethiol (0·25 c.c.) added to the suspension. The juglone rapidly dissolved forming a brown solution, followed almost immediately by a yellow-brown crystalline precipitate. The mixture was heated just to the boiling point and allowed to cool. Almost pure

3-phenylthiojuglone separated and was recrystallised from alcohol; it formed orange-yellow needles, m. p. 153° (yield, 80%).

(*b*) A solution of benzenethiol (0·26 c.c.) in alcohol (5 c.c.) containing pyridine (0·2 c.c.) was added to a suspension of 3-chlorojuglone (0·5 g.) in alcohol (30 c.c.). The quinone rapidly dissolved with evolution of heat followed by deposition of 3-phenylthiojuglone. The suspension was heated to the boiling point and the dark-red solution then allowed to cool. The *juglone* which separated was recrystallised from alcohol forming orange-yellow needles, m. p. 153° (yield, 60%) (Found: C, 68·0; H, 3·4. $C_{16}H_{10}O_3S$ requires C, 68·1; H, 3·6%). The *acetate* separated from alcohol in long yellow needles or plates, m. p. 156° (Found: C, 67·0; H, 3·8. $C_{18}H_{12}O_4S$ requires C, 66·7; H, 3·7%). Reductive acetylation of the acetate afforded 1 : 4 : 5-*triacetoxy*-3-*phenylthionaphthalene* which crystallised from aqueous alcohol in small needles, m. p. 131° (Found: C, 64·3; H, 4·3. $C_{22}H_{18}O_6S$ requires C, 64·4; H, 4·4%).

2-*Methyl*-3-p-*tolylthiojuglone*.—A solution of toluene-*p*-thiol (0·8 g.) in alcohol (12 c.c.) containing pyridine (0·53 c.c.) was added to a suspension of 3-chloro-2-methyljuglone (1·45 g.) in alcohol (60 c.c.). The mixture was refluxed for 1 hour and set aside overnight. The crystalline product was collected and recrystallised from alcohol (charcoal) forming clusters of reddish-brown needles, m. p. 126°, of the *juglone* (yield 76%) (Found: C, 70·0; H, 4·8. $C_{18}H_{14}O_3S$ requires C, 69·7; H, 4·5%). The *acetate* formed red needles (from alcohol), m. p. 148° (Found: C, 67·9; H, 4·5. $C_{20}H_{16}O_4S$ requires C, 68·2; H, 4·5%). Reductive acetylation of the quinone gave 1 : 4 : 5-*triacetoxy*-2-*methyl*-3-p-*tolylthionaphthalene* forming small needles (from aqueous acetic acid), m. p. 184° (Found: C, 65·9; H, 5·2. $C_{24}H_{22}O_6S$ requires C, 65·75; H, 5·0%).

3-*Carboxymethylthio*-2-*methyljuglone*.—A solution of 3-chloro-2-methyljuglone (1·93 g.), thioglycollic acid (0·6 c.c.), and pyridine (2·2 c.c.) in alcohol (110 c.c.) was boiled for 2 minutes and then set aside overnight. After acidification with 4N-sulphuric acid, the solution was cooled in an ice-bath, stirred, and diluted with water (400 c.c.). Stirring was continued until the oily precipitate had crystallised. The product was collected, washed, dried, and recrystallised from benzene–light petroleum (charcoal). The *acid* separated in minute bright-red needles, m. p. 168° (yield, 58%) (Found: C, 56·1; H, 3·9. $C_{13}H_{10}O_5S$ requires C, 56·1; H, 3·9%). The *ethyl* ester was obtained by boiling a solution of the acid (0·6 g.) in alcohol (25 c.c.) with concentrated hydrochloric acid (8 c.c.) for 2 minutes. It crystallised from aqueous alcohol in orange-yellow needles, m. p. 94° (Found: C, 58·8; H, 4·7. $C_{15}H_{14}O_5S$ requires C, 58·8; H, 4·6%).

3-*Ethylthiojuglone*.—A solution of 3-chlorojuglone (0·4 g.) in alcohol (20 c.c.) containing ethanethiol (0·2 c.c.) and pyridine (0·5 c.c.) was boiled for 1 minute and set aside to crystallise. 3-*Ethylthiojuglone* separated from alcohol in orange needles, m. p. 152° (yield, 36%) (Found: C, 61·55; H, 4·3. $C_{15}H_{10}O_3S$ requires C, 61·55; H, 4·3%). The *acetate* formed fine yellow needles (from alcohol), m. p. 157° (Found: C, 60·7; H, 4·4. $C_{14}H_{12}O_4S$ requires C, 60·85; H, 4·4%). 3-Ethylthiojuglone could not be obtained by addition of ethanethiol to juglone.

3-*Ethylthio*-2-*methyljuglone*.—This was prepared in the usual way from 3-chloro-2-methyljuglone (0·42 g.), ethanethiol (0·2 c.c.), and pyridine (0·5 c.c.) in alcohol (20 c.c.), and isolated by acidification of the solution and dilution with water. 3-*Ethylthio*-2-*methyljuglone* crystallised from aqueous alcohol in fine orange needles, m. p. 85° (yield, 38%) (Found: C, 63·05; H, 5·2. $C_{13}H_{12}O_3S$ requires C, 62·85; H, 4·9%). The *acetate* formed fine yellow needles (from aqueous alcohol), m. p. 91° (Found: C, 62·1; H, 5·15. $C_{15}H_{14}O_4S$ requires C, 62·05; H, 4·85%).

2-*Methyljuglone* (*Plumbagin*).—3-Carboxymethylthio-2-methyljuglone (1·4 g.) in alcohol (70 c.c.) was refluxed with Raney nickel (7 g.) for 10 minutes. After addition of a little "Celite" and a few drops of glacial acetic acid, the hot suspension was filtered rapidly into a solution of stannous chloride (7 g.) in water (252 c.c.) containing concentrated hydrochloric acid (28 c.c.). The nickel residue was extracted four times with boiling alcohol (70 c.c. in all). The alcohol was removed from the combined filtrates by distillation, and the residual acid solution heated with a little charcoal and filtered. After extraction of the pale yellow filtrate with chloroform (4 × 5 c.c.) the aqueous solution of α-hydroplumbagin was cooled in ice, and hydrogen peroxide (16 c.c.; 100 vols.) added. After 1 hour the fine orange crystalline precipitate of plumbagin was collected and dried *in vacuo* (0·49 g.; m. p. 71—73°). Ether-extraction of the filtrate yielded a further small quantity of the quinone, which crystallised from aqueous alcohol in orange-yellow needles, m. p. 77°; total yield 48% (Fieser and Dunn, *loc. cit.*, give m. p. 78—79°; Dieterle and Kruta, *loc. cit.*, give m. p. 77°) (Found: C, 70·05; H, 4·45. Calc. for $C_{11}H_8O_3$: C, 70·2; H, 4·3%). The acetate separated from aqueous alcohol in small yellow needles, m. p. 117—118° (Found: C, 68·0; H, 4·4. Calc. for $C_{13}H_{10}O_4$: C, 67·8; H, 4·4%). The chloroform extract was dried ($CaCl_2$) and the solvent removed under reduced pressure. Crystallisation of the residue from light petroleum (b. p. 100—120°) afforded fine pale yellow needles, m. p. 164° (*ca.* 5 mg.) (Found: C, 68·9, 68·8; H, 6·6, 6·5%).

1 : 2 : 3 : 4-*Tetrahydro*-5-*hydroxy*-1 : 4-*diketo*-2-*methylnaphthalene* (β-*Hydroplumbagin*).—This was prepared by Madinaveitia and Olay's method (*Anal. Fis. Quim.*, 1933, **31**, 134) of fusing the α-isomer in a vacuum. It formed small, pale-yellow needles, m. p. 87° (the Spanish workers report 86°) (yield, 41%) [Found: C, 69·3; H, 5·1; Active H, 0·40.* Calc. for $C_{11}H_{10}O_3$: C, 69·45; H, 5·3; Active H (one atom), 0·53%].

I am indebted once again to Dr. W. C. Price and Mr. T. S. Robinson for the infra-red absorption data and to Dr. C. Daglish for the ultra-violet absorption curve. Analyses are by Mrs. M. A. B. Fyfe.

MARISCHAL COLLEGE, ABERDEEN. [*Received, December 27th*, 1950.]

* Analysis by Drs. Weiler and Strauss.

276. *The Constitution of a Pear Cell-wall Xylan.*

By S. K. Chanda, E. L. Hirst, and E. G. V. Percival.

A xylan from the cell-wall of ripe "Conference" pears has been investigated. The polysaccharide was devoid of arabinose residues. Methylation and hydrolysis gave trimethyl D-xylopyranose (*ca.* 2%) corresponding to the presence of one non-reducing end group in 55—60 xylose units. In addition to 2 : 3-dimethyl xylose (91%), 2-methyl xylose (*ca.* 2%) and a tetramethyl aldobiuronic acid (*ca.* 2%) were also isolated. To this last product is assigned the constitution 2-methyl 3-[2 : 3 : 4-trimethyl α-D-glucuronosido]-D-xylose.

A branched structure is proposed for the xylan which appears to have 115 (±5) D-xylopyranose units in a chain with a single branch (cf. esparto xylan, *J.*, 1950, 1289) but carrying in addition a terminal D-glucopyruronic acid residue at one point. A determination of the molecular weight of the methylated xylan by the osmotic-pressure method and other observations agree with the above interpretation.

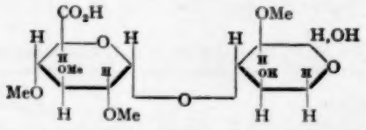
As a result of our recent study of esparto xylan (Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1289), it was concluded that this polysaccharide is constructed exclusively of D-xylopyranose units, about eighty of which, linked through the 1 : 4-positions, are disposed in a singly-branched structure with the bifurcation involving the hydroxyl group on $C_{(3)}$ of one of the xylopyranose residues. The molecule thus contained one reducing and two non-reducing terminal groups.

While this work was proceeding, Dr. F. A. Isherwood and Dr. M. A. Jermyn of the Low Temperature Research Station, Cambridge, isolated from the cell-wall material of ripe pears another type of xylan devoid of arabinose residues, and kindly placed a quantity of this material at our disposal for structural investigations.

The xylan, $[\alpha]_D^{19}$ −86° (*c*, 0·6 in 0·5N-sodium hydroxide), on hydrolysis and estimation by filter-paper chromatography gave xylose in 97% yield. The presence of a uronic acid in the hydrolysate could not be conclusively determined; chromatographic separation on a heavily spotted paper, however, gave a very faint spot which corresponded possibly with glucuronic acid but could not be confirmed directly by the naphtharesorcinol test on the hydrolysate.

Methylation and fractionation of the product gave a methylated derivative {$[\alpha]_D^{19}$ −71° (in chloroform); yield 90%}. The methylated polysaccharide was hydrolysed with methanolic hydrogen chloride giving the glycosides, and from them the free sugars were obtained by hydrolysis with dilute hydrochloric acid. The hydrolysed sugars were separated on the cellulose column and the following fractions obtained: (*a*) trimethyl pentose (*ca.* 2%); (*b*) 2 : 3-dimethyl xylose (*ca.* 91%); and (*c*) 2-methyl xylose (*ca.* 2·3%) and an aldobiuronic acid (*ca.* 2·3%). The trimethyl pentose and the monomethyl xylose were both crystalline, and were identified as 2 : 3 : 4-trimethyl D-xylose and 2-methyl D-xylose respectively, confirmation being obtained by forming the anilides. The 2 : 3-dimethyl D-xylose was identified as its anilide, and as the lactone, amide, and *p*-bromophenylhydrazide of the corresponding 2 : 3-dimethyl xylonic acid.

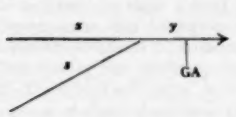
The aldobiuronic acid was identified as 2-methyl 3-(2 : 3 : 4-trimethyl α-D-glucuronosido)-D-xylose in the following way. Examination on the paper chromatogram showed the heart-shaped pattern characteristic of uronic acids (Partridge, *Biochem. J.*, 1948, **42**, 238; Reid, *J. Sci. Food Agric.*, 1950, **1**, 234). Treatment with hydrobromic acid (Hough, Jones, and Wadman, *J.*, 1950, 1702) yielded xylose and 2-methyl xylose. Reduction with lithium aluminium hydride (Lythgoe and Trippett, *J.*, 1950, 1983) followed by hydrolysis and examination on the paper chromatogram gave 2-methyl xylose and 2 : 3 : 4-trimethyl glucose in practically equimolar proportion. The equivalent weight of the methylated aldobiuronic acid (395) was, in view of its hygroscopic nature, reasonably close to the theoretical value of 382, and the high rotation ($[\alpha]_D^{20}$ +108·5°) strongly suggested an α-glycosidic linkage:



Such a compound would require one equivalent of periodate for oxidation and should give rise to a molecule of formaldehyde but no formic acid. In practice, 0·7 mole of periodate was utilised

in 24 hours and formaldehyde, but no formic acid, was produced. The alternative possibility of a linkage to $C_{(4)}$ of the xylose residue is, therefore, discounted since no attack by periodate could occur in that case.

The paper-chromatographic estimation of the different sugars obtained on hydrolysis by hypoiodite oxidation showed the following molar percentage composition: 2 : 3 : 4-trimethyl xylose (1·8—1·9), 2 : 3-dimethyl xylose (96·2—96·5) and 2-methyl xylose (1·6—1·8). A chain of 55 xylose units with one non-reducing terminal group would give trimethyl xylopyranose amounting to 1·95% of the free sugars produced on hydrolysis. The proportion of 2-methyl xylose is also of the same order but it is not to be supposed that the whole of this is derived from branching points in the xylan molecule: demethylation during hydrolysis and incomplete methylation of the starting material have to be taken into account also. As reported previously (*loc. cit.*), 2 : 3-dimethyl xylose gave only 0·3% of monomethyl xylose when treated under the hydrolytic conditions employed for methylated esparto xylan, so that the contribution from the



$x + y + z = 115 \pm 5$.
⟶ = reducing group.

FIG. 1.

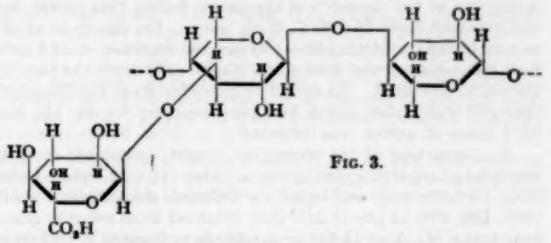
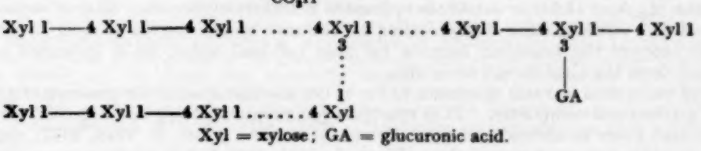


FIG. 3.



Xyl = xylose; GA = glucuronic acid.

FIG. 2.

first source must be small. It is highly probable, however, that incomplete methylation is responsible for at least half of the 2-methyl xylose detected, although it would be quite impossible to detect this by the micro-Zeisel methoxyl determination. Clearly if all the 2-methyl xylose estimated to be present in the hydrolysate had a structural significance it would be necessary to suppose the pear cell-wall xylan molecule to contain nearly as many branch points as non-reducing terminal groups, and the molecule would, therefore, contain several unit chains. There is, however, independent evidence for the conclusion that only two chains of *ca.* 55 xylose units make up the structure of the pear cell-wall xylan. The most definite is the result of the determination of the molecular weight by osmotic-pressure method (by courtesy of Mr. G. Forsyth of this Department through the co-operation of Professor H. W. Melville, F.R.S., at Birmingham University) which gave a value of 17,500 (degree of polymerisation *ca.* 110). On the basis of the above results the xylan molecule will consist of one reducing and two non-reducing terminal positions. The occurrence of an aldobiuronic acid constructed from 2-methyl xylose and trimethyl glucuronic acid also indicated that the latter is linked as a side chain in the molecule through $C_{(3)}$ of a xylose residue. One of the possible representations is given in Figs. 1 and 2, and the linkage of the D-glucuronic acid residue to the chain of D-xylopyranose units is shown in Fig. 3.

It may be recalled that a similar type of structure was proposed for esparto xylan (Chanda *et al.*, *loc. cit.*) although the maximum number of xylose residues in the molecule was estimated to be 80 in that case and no uronic acid was attached to the chain.

It should be noted that the glucuronic acid residue may be situated on any of the xylose units except the non-reducing terminal groups and the branching point.

In the present instance the type of structure proposed receives support from the estimate of the reducing power determined by the reduction of 3 : 5-dinitrosalicylic acid in alkaline solution (Meyer *et al.*, *Helv. Chim. Acta*, **1948**, **31**, 103), which, applied as described previously (Chanda *et al.*, *loc. cit.*), indicated the presence of one reducing group in 110—115 units in pear

cell-wall xylan compared with one in 70—80 units in esparto xylan. On the other hand the estimation of reducing power by the hypoiodite oxidation method gave a result corresponding to 42 residues per reducing group, but a similar estimation also gave an anomalous result with esparto xylan.

The interpretation of the results of periodate oxidation is not as straightforward as in the case of the xylan from esparto grass. Pear cell-wall xylan was completely oxidised by sodium metaperiodate, consuming 1·02 mols. per $C_5H_8O_4$ residue, but it required 144 hours to oxidise the polysaccharide, as against 48 hours in the case of xylan from esparto grass. The liberation of formic acid on oxidation with potassium metaperiodate also took a different course. Even after 366 hours formic acid was still gradually accumulating, whereas the esparto xylan was completely oxidised in less than 200 hours and β-methylxylopyranoside required only 150 hours. Although the continued slow release of formic acid is a characteristic of compounds containing uronic acid groups it makes impossible a precise estimate of the molecular size by the periodate method. Nevertheless, a value taken within the range of 150—200 hours, or that given by the projection of the tangents of the curve during this period, indicated that 1 mole of formic acid was released from 18—20 $C_5H_8O_4$ units. On the type of structure proposed this corresponds to a molecule containing 90—100 pentose residues, since 2 mols. of formic acid would be released from the reducing end group and 1 mol. each from the two non-reducing xylose end groups and the glucuronic acid. As would be expected from the branched structure, after the hydrolysis of pear cell-wall xylan which had been oxidised for *ca.* 150 hours with sodium periodate a very faint trace of xylose was detected.

A comparison of the molecular weight, calculated from the specific viscosity, with that of methylated esparto xylan shows a value [41—42 xylose residues by use of the constant $K_m = 12 \times 10^{-4}$ formerly employed for cellulose derivatives by Staudinger and Reinecke (*Annalen*, 1938, **535**, 47)] of about half that obtained from esparto grass, whereas the specific viscosity of pear xylan ($\eta_{sp.}/c = 11{\cdot}34$) in N-sodium hydroxide is slightly higher than that of esparto xylan ($\eta_{sp.}/c = 9{\cdot}8$). Although the interpretation of viscosity measurements is open to doubt, this tends to support the branched formula for pear cell-wall xylan, as it indicated a further divergence from the ideal thread molecules.

One of the special features of interest in the xylan now discussed is the presence of glucuronic acid as a structural component. It is true that glucuronic acid appears together with xylose in such plant gums as almond-tree gum (Brown, Hirst, and Jones, *J.*, 1948, 1677), peach gum (Jones, *J.*, 1950, 534), and many others (Hirst, *J.*, 1949, 522), but in all these cases other sugar building units such as galactose, arabinose, and rhamnose are present also. Examples of polysaccharides containing xylose and glucuronic acid residues as the sole building components, a point of importance in connection with the suggestion that pentoses may originate by the decarboxylation of the corresponding hexuronic acids, are much fewer in number. One may recall the polysaccharide from *Kadzura japonica* (Nishida, Hashima, and Fukamizu, *J. Agric. Chem. Soc. Japan*, 1934, **10**, 1001; 1935, **11**, 261) and the hemicelluloses of the English oak (O'Dwyer, *Biochem. J.*, 1939, **33**, 713; 1940, **34**, 149) and the cottonwood, *Populus macdougali* (Anderson *et al.*, *J. Biol. Chem.*, 1942, **144**, 767), although in these cases a methoxyglucuronic acid is involved. The example about which most is known from the structural viewpoint is the polyuronide hemicellulose of New Zealand flax (*Phormium tenax*) (McIlroy, Holmes, and Mauger, *J.*, 1945, 796; McIlroy, *J.*, 1949, 121). In this polysaccharide the glucuronic acid residue was shown to occupy the position of a non-reducing end group as in our xylan, although the method of attachment to a relatively short main chain of xylopyranose residues linked through $C_{(1)}$ and $C_{(4)}$ appears to involve the intervention of another xylopyranose unit. It is clear that further investigations will be of great interest in view of the present deficiencies in our knowledge of the group of xylose–glucuronic acid polysaccharides.

Experimental.

The polysaccharide was prepared, and kindly made available to us, by Dr. F. A. Isherwood and Dr. M. A. Jermyn of the Low Temperature Research Station, Cambridge. The method of extraction carried out may briefly be described: Ripe "Conference" pears were peeled, cored, and frozen at −20°. The product was ground and added to sufficient boiling alcohol to give a final concentration of 90%. After an hour's boiling under reflux the residual material was filtered off and extracted two or three times with boiling 95% alcohol to remove the last traces of free sugars. The material was then broken up, and dried in the air to a powder, and finally at 100° to constant weight. The yield was 2·4% on the dressed weight of pears. The cell-wall material contained large amounts of water-soluble "pectin." It was freed from pectin by boiling it with water (4 l./100 g.). A twelve hours' extraction, followed by 3—4 periods of four hour's extraction, was usually sufficient for this purpose. The material was dried

as before (yield, 70·3%). The holocellulose was prepared from the depectinised cell-wall material (lignin 23·1, and ash 0·9%) by treatment with acidified (pH 4—5) sodium chlorite solution at 70—80° (Wise *et al.*, *Paper Trade J.*, 1946, **126**, 35). The xylan was extracted from the holocellulose by 24% potassium hydroxide solution and was precipitated by potassium Benedict solution (*i.e.* Benedict solution made with potassium instead of sodium salts). The copper complex thus formed was decomposed by glacial acetic acid, washed with 80% acetic acid to free it from copper followed by acetone, to remove the acid, and ether (yield, 25·9% on the carbohydrate content of the original holocellulose). The crude xylan (30 g.; xylose 90, glucose 7, galactose 3%, and a trace of arabinose estimated on a paper chromatogram) was purified by precipitation twice as the copper complex and regeneration of the xylan as just described. The pure polysaccharide (24·1 g.) had a low ash (0·4%) and copper content (0·018%).

Separation of the Water-soluble Fraction.—The xylan (12 g.) was treated with water (200 c.c.), with shaking, for 24 hours to extract any water-soluble fraction. The solution was centrifuged and the insoluble fraction dried by washing it with alcohol and ether and finally over phosphoric oxide in a vacuum-desiccator (98·5%). The aqueous solution was slightly turbid, and gave a precipitate with excess of alcohol (1·5% yield). The insoluble polysaccharide had $[\alpha]_D^{19}$ −86° (*c*, 0·6 in 0·5N-sodium hydroxide).

Identification and Estimation of Xylan Hydrolysate.—Filter-paper chromatographic examination (Partridge, *loc. cit.*) of the xylan hydrolysate indicated the presence of xylose—a developed paper showed a brown spot with ammoniacal silver nitrate, a pink spot with aniline oxalate, and a blue spot with naphtharesorcinol in dilute hydrochloric acid. Glucuronic acid was also detected as a faint spot in a heavily spotted paper, but could not be confirmed by naphtharesorcinol test on the hydrolysate. Chromatographic estimation of the xylose obtained on hydrolysis with 0·5N-sulphuric acid by both Somogyi's copper reagent (Flood, Hirst, and Jones, *J.*, 1948, 1679) and hypoiodite oxidation (Chanda, Hirst, Jones, and Percival, *loc. cit.*) accounted for 96—97% of xylan.

Methylation.—The xylan (9 g.) was methylated in a nitrogen atmosphere by two series of five methylations, each with methyl sulphate and sodium hydroxide (Chanda *et al.*, *loc. cit.*). The methylated polysaccharide (8·5 g.) had $[\alpha]_D^{19}$ −72° in chloroform (*c*, 1) and OMe, 38·4% (Calc. for $C_7H_{12}O_4$: OMe, 38·75%).

Methylation by methyl iodide and silver oxide. The polysaccharide was almost completely methylated by sodium hydroxide and methyl sulphate. To see whether the methoxyl content could be further increased, the above methylated xylan (8·5 g.) was dissolved in methyl iodide (200 g.) in the presence of methanol (10 c.c.) and boiled gently in the presence of silver oxide (100 g.) for 24 hours. The solution was then filtered and the oxide was repeatedly washed with hot chloroform. The filtrate on concentration gave a yellowish solid (8·4 g.). It was purified by dissolution in chloroform and precipitation with excess of dry ether. The colourless precipitate, filtered off and dried (97%), had $[\alpha]_D^{14}$ −71·5° in chloroform (*c*, 1) and OMe, 38·9%. The filtrate on concentration gave a little brown syrup (3%).

Fractionation of Methylated Xylan.—The methylated xylan (7 g.) was fractionated by various mixtures of chloroform and purified light petroleum (b. p. 65—66°) (Chanda *et al.*, *loc. cit.*). As in the case of xylan from esparto grass, with increasing concentration of chloroform in petroleum the removal of a syrup (acetone condensation product) is effected, leaving a highly purified methylated polysaccharide. The syrupy fraction had been removed during purification and also the preliminary investigation showed that very little was soluble in a solvent mixture having 15% or less of chloroform. The methylated polysaccharide started swelling in 20 : 80 chloroform–petroleum, and the polysaccharide was completely soluble in 30 : 70 chloroform–petroleum. The results are collected in the following Table.

Fraction.	Solvent, chloroform–light petroleum.	Yield, %.	Sulphated ash, %.	OMe, %.	$[\alpha]_D^{19}$.
1	20 : 80	2·3	0·12	38·6	—
2	25 : 75	6·9	0·14	38·5	−67°
3 *	30 : 70	90·5	0·19	38·7	−71°

* Fraction 3, Found: C, 52·2; H, 7·1. Calc. for $C_7H_{12}O_4$: C, 52·5; H, 7·5%.

Hydrolysis of Methylated Xylan and Separation of Methylated Xyloses.—(a) *Paper partition chromatography.* The polysaccharide (100 mg.) was hydrolysed successively with methanolic hydrogen chloride (5 c.c.; 1%) and aqueous hydrochloric acid (10 c.c.; 0·5N.) (Chanda *et al.*, *loc. cit.*), neutralised with silver carbonate, and filtered, and the silver and other basic ions were removed from the filtrate by hydrogen sulphide and " Amberlite IR100 H " ion-exchange resin. The clear solution was concentrated to a thin syrup at 35°/15 mm. Examination on a paper chromatogram with butanol–ethanol–water (4 : 1 : 5) showed, on development with aniline oxalate and ammoniacal silver nitrate, three distinct spots corresponding to a trimethyl pentose (R_G, 0·94—0·95), 2 : 3-dimethyl xylose (R_G, 0·75—0·76) and a monomethyl xylose (R_G, 0·38—0·40). A fourth sugar travelling just ahead of the starting line in the above solvent, but as far as midway between 2-methyl xylose and 2 : 3-dimethyl xylose in butanol–acetic acid–water (4 : 1 : 5), was also identified. The aniline oxalate spray showed it as a cherry-coloured heart-shaped spot characteristic of uronic acids (Partridge, *loc. cit.*; Reid, *loc. cit.*). Silver nitrate indicated a white patch on a light brown background.

The three pentoses were estimated by alkaline hypoiodite oxidation after separation on a paper chromatogram (Chanda *et al.*, *loc. cit.*) (see Table).

Sugar.	Experiment 1. Wt., mg.	Experiment 1. Molar composition, %.	Experiment 2. Wt., mg.	Experiment 2. Molar composition, %.
2 : 3 : 4-Trimethyl xylose	0·21	1·8	0·23	1·9
2 : 3-Dimethyl xylose	10·31	96·5	10·50	96·2
2-Methyl xylose	0·16	1·6	0·19	1·8

The uronic acid travelling close to the starting line did not consume any appreciable quantity of iodine. The chain length calculated on the above results indicate one non-reducing end group per 52—55 xylose units.

(b) *By the cellulose column.* Methylated xylan (5 g.) was hydrolysed on a water-bath with methanolic hydrogen chloride (500 c.c.; 1%) and the rotation observed: $[\alpha]_D^{13}$ +14° (2 hours), 36° (3 hours), 62° (4 hours), 78° (5 hours), 84° (6 hours, constant). It was observed that when the solution was kept overnight the specific rotation of the hydrolysed solution changed to +76° but, when the solution was again heated for an hour and cooled, the observed rotation corresponded to the value obtained during hydrolysis: $[\alpha]_D$ +84° ⟶ +76° in 24 hours.

The solution was neutralised with silver carbonate and filtered. The filtrate was concentrated to a syrup and dried in a vacuum-desiccator over phosphoric oxide at room temperature (6·1 g.). The syrup was rehydrolysed at 95° with hydrochloric acid (250 c.c.; 0·5N.), the rotations observed being $[\alpha]_D^{19}$ +60° (0 hour), 56·5° (1 hour), 45° (2 hours), 40° (3 hours), 36·5° (4 hours), 32·8° (5 hours), 31·5° (6 hours), 29·5° (7 hours), 29·1° (8 hours, constant). The acid solution was neutralised with silver carbonate, triturated with water, and filtered, silver ions were removed with hydrogen sulphide, and the syrup was obtained in the usual way (5·6 g.).

This syrup was separated on a column (60 × 4 cm.) of powdered cellulose (Hough, Jones, and Wadman, *J.*, 1949, 2511; Chanda, Hirst, Jones, and Percival, *loc. cit.*). The solvent employed for elution was purified light petroleum (b. p. 100—120°)–*n*-butanol (7 : 3) saturated with water. The eluate was collected in 5-c.c. batches in the automatic device which changed the tubes every 4 minutes. A fraction of the contents of each tenth tube was evaporated and the residue, if any, analysed on the paper chromatogram in chronological order. 2 : 3 : 4-Trimethyl xylose, 2 : 3-dimethyl xylose, and monomethyl xylose were completely separated from each other. Monomethyl xylose travelled slowly through the cellulose column with the above petroleum mixture, so the mobile phase was changed to *n*-butanol (100 c.c.), followed by butanol partly saturated (50% saturation) with water after the dimethyl xylose had been separated out. The tubes were then grouped to contain a pure sugar, and the solution was concentrated at 35°/15 mm. to a syrup, and dissolved in water, some waxy material separating. It may be mentioned that the formation of such waxy material could be avoided when the butanol used for separation was purified by being boiled under reflux over sodium hydroxide and distilled (unpublished). The solution was treated with a little charcoal and filtered through a well-washed bed of "Filter Cel," and the clear solution was again concentrated. The syrup was further purified by dissolving it in acetone or hot methanol when necessary, filtered, concentrated, and left to crystallise in a refrigerato (see Table).

Fraction.	Tube no.	Sugar.	Wt. (g.).
—	1—35	No sugar	—
1	36—80	Trimethyl pentose	0·1481
2	81—240	2 : 3-Dimethyl xylose	4·8120
—	241—354	No sugar	—
3	355—480	Monomethyl xylose	0·1200
—	481—600	Xylose	trace
4	Water wash	Aldobiuronic acid	0·1410

Examination of the Fractions.—Fraction 1. The syrup (148·1 mg.) did not crystallise even on long storage. Chromatographic examination showed only one spot corresponding to a trimethyl pentose. It had OMe, 46·5 (Calc. for $C_8H_{16}O_5$: OMe, 48·4%) and hypoiodite oxidation indicated 70% of pure aldopentose: $[\alpha]_D^{18}$ +25·3° in water (*c*, 1·16) in the presence of a trace of acid. A little syrup (10 mg.) was rehydrolysed with 0·5N-hydrochloric acid, and the sugar was regenerated as usual. Paper-chromatographic examination of this hydrolysed sugar showed the presence of 2 : 3-dimethyl xylose along with the original trimethyl pentose. This observation coupled with the methoxyl content and hypoiodite oxidation showed that the syrup probably contained some (*ca.* 30%) 2 : 3-dimethyl methylxyloside.

The syrup (128·2 mg.) was rehydrolysed with hydrochloric acid (10 ml.; 3%) on a water bath for 5 hours. $[\alpha]_D^{18}$ +25° (0 hour), 22·6° (2 hours), 21·8° (3 hours), 21° (4 hours, constant) was observed. The solution was neutralised with silver carbonate, and the sugar obtained in the usual way (124 mg.).

Column separation of the mixture (semi-micro scale). Quantitative separation of the sugar mixture was effected in a long but narrow column (55 cm. × 1·5 cm.). The column was packed and washed as before. The syrup was soaked in at the top and the column was developed with light petroleum–butanol (7 : 3). The rate of the eluate coming out was slow but steady, and 5 c.c. were collected in 24 minutes. The chromatographic examination of the collected eluates showed that the two sugars were effectively separated. They were concentrated and purified as before. The results are summarised in the following Table.

Sugar.	Wt. (mg.).	$[\alpha]_D^{14}$.	Sugar by hypoiodite oxidation (%).	OMe (%).
Trimethyl pentose	83·2	+19·9°	97·2	48·3
2 : 3-Dimethyl xylose	35·8	+21°	92·0	33·2

The trimethyl pentose syrup crystallised completely in a day when seeded with 2 : 3 : 4-trimethyl xylose. The crystalline mass (m. p. 86°) was recrystallised from dry ether; 4 crops in almost quantitative yield were obtained, of m. p. 90° alone or on admixture with a specimen of trimethyl D-xylopyranose (Found : C, 49·2; H, 8·2. Calc. for $C_8H_{16}O_5$: C, 50·0; H, 8·3%).

Examination by the *X*-ray powder photograph method, by the kindness of Dr. C. A. Beevers, showed the substance to be trimethyl xylopyranose. The derived anilide had m. p. 103° alone or on admixture with an authentic specimen (Found : C, 63·0; H, 7·9; N, 5·2; OMe, 33·2. Calc. for $C_{14}H_{21}O_4N$: C, 62·9; H, 7·8; N, 5·2; OMe, 34·8%).

2 : 3-Dimethyl xylose (35·8 mg.) was identified by means of the anilide which gave the same m. p. (143°) as 2 : 3-dimethyl xylose anilide alone or admixed (Found : OMe, 23·7. Calc. for $C_{13}H_{19}O_4N$: OMe, 24·5%).

The amount of pure trimethyl D-xylopyranose obtained was nearly 100 ± 10 mg., corresponding to one non-reducing end group in 60 ± 5 xylose units.

Fraction 2. The syrup (4·81 g.) had $[\alpha]_D^{15}$ +22·8° (*c*, 2·95 in water), η_D^{15} 1·4760 (Found : OMe, 34·0. Calc. for $C_7H_{14}O_5$: OMe, 34·8%). Hypoiodite oxidation indicated 98—99% of aldopentose and chromatographic examination showed only 2 : 3-dimethyl xylose. The derived anilide had m. p. 145° alone or admixed with an authentic specimen and $[\alpha]_D^{15}$ +186° ⟶ +73° (45 minutes, constant; *c*, 0·9 in ethyl acetate containing 5% v/v acetic acid) (Found : C, 61·6; H, 7·5; N, 6·0; OMe, 24·1. Calc. for $C_{13}H_{19}O_4N$: C, 61·6; H, 7·6; N, 5·5; OMe, 24·5%).

Fraction 2 was converted into its furanolactone, $[\alpha]_D^{15}$ +96·5°, η_D^{15} 1·4670 (Found : OMe, 35·1. Calc. for $C_7H_{12}O_5$: OMe, 35·2%). Methanolic anhydrous ammonia quantitatively converted the lactone into the amide which crystallised on removal of the solvent. It was recrystallised from ethyl acetate and had m. p. 133° (alone or on admixture with an authentic specimen), $[\alpha]_D^{15}$ +48° in water (*c*, 0·84) (Found : C, 43·6; H, 7·8; N, 7·0; OMe, 31·6. Calc. for $C_7H_{14}O_5N$: C, 43·5; H, 7·7; N, 7·25; OMe, 32·1%).

2 : 3-Dimethyl D-xylono-*p*-bromophenylhydrazide (85% yield) had m. p. 150° (alone or on admixture with an authentic specimen) and $[\alpha]_D^{15}$ +24° (*c*, 1·22 in ethanol). No mutarotation could be observed in the presence of acid (Found : C, 43·8; H, 5·3; N, 7·8; Br, 21·6; OMe, 16·1. Calc. for $C_{13}H_{19}O_4N_2Br$: C, 43·0; H, 5·3; N, 7·7; Br, 22·0; OMe, 17·1%).

Fraction 2 was, therefore, pure 2 : 3-dimethyl D-xylose.

Fraction 3. The syrup (120 mg.) crystallised completely when seeded with 2-methyl D-xylopyranose. Chromatographic examination indicated the presence of the above sugar only. The crude crystals had $[\alpha]_D^{15}$ +28° (*c*, 1 in water), and hypoiodite oxidation indicated 96% purity. Recrystallised from methanol, it had m. p. 133° alone or on admixture with an authentic specimen (Found : C, 44·0; H, 7·6; OMe, 17·5. Calc. for $C_8H_{15}O_5$: C, 43·9; H, 7·3; OMe, 18·9%). The derived anilide had m. p. 124° alone or on admixture with an authentic specimen (Found : C, 59·6; H, 7·2; N, 5·5; OMe, 13·2. Calc. for $C_{12}H_{17}O_4N$: C, 60·25; H, 7·1; N, 5·85; OMe, 13·0%).

Fraction 4. This was a hygroscopic solid. It was purified by dissolving it (141 mg.) in hot methanol. Chromatographic examination indicated two cherry-coloured coalescing spots (R_G nearly 0·1) when a paper was irrigated with *n*-butanol–ethanol–water (4 : 1 : 5) and developed with aniline oxalate; when a similar paper was irrigated with acid solvent (*n*-butanol–acetic acid–water; 4 : 1 : 5) the spots travelled as far as 2 : 3-dimethyl xylose (distance travelled 14·3 and 16 cm. when 2 : 3-dimethyl xylose travelled 15·1 cm.). The spot having the smaller R_G value showed a heart-shaped pattern in both the solvents characteristic of uronic acid (Partridge, *loc. cit.*; Reid, *loc. cit.*), but the spots did not correspond to any methylated galacturonic acids obtained by the hydrolysis of methylated pectic acid.

Heavy spotting, however, indicated that the fraction 4 contained traces of 2-methyl xylose and xylose. It (130 mg.) was purified by passage again through a semimicro-column of cellulose (*loc. cit.*). The solvent used for the eluate was the organic fraction of the mixture butanol–acetic acid–water (4 : 1 : 5). The various fractions identified and obtained in the usual way were : (*a*) unidentified uronic acid (121·4 mg.), purified by extraction with hot methanol (110·2 mg.); (*b*) mixture of (*a*) and 2-methyl xylose (2·9 mg.); (*c*) 2-methyl xylose (1·4 mg.); and (*d*) xylose (2·1 mg.).

Demethylation of the fraction (4*a*; 10 mg.) with hydrobromic acid (Hough, Jones, and Wadman, *J.*, 1950, 1702) and examination of the demethylated product on the paper chromatogram indicated the presence of 2-methyl xylose and xylose. 2 : 3-Dimethyl xylose was also very faintly indicated but could not be confirmed.

Reduction with lithium aluminium hydride. The fraction (4*a*; 10—20 mg.) was heated in a sealed tube for 5 hours with methanolic hydrogen chloride (1%; 2 c.c.). The solution was neutralised with dry ethereal diazomethane. It was evaporated to dryness at 40°/15 mm., dissolved in dry ether (10 c.c.), and treated with an equal volume of an ethereal solution of lithium aluminium hydride (0·1 g.) (Lythgoe and Trippett, *J.*, 1950, 1983). The solution was refluxed gently for 3 hours, then cooled, and the excess of hydride was carefully destroyed with water. The solution was acidified with 2N-sulphuric acid and extracted repeatedly (10—15 times) with chloroform. The organic fraction was concentrated to a syrup at 30°/15 mm. and hydrolysed with 0·5N-hydrochloric acid (10 c.c.; 7 hours). It was neutralised with silver carbonate, and the soluble silver removed from the solution as described before. The solution was aerated and treated with " Amberlite IR100 H " to remove the basic ions, and concentrated to a thin syrup. Paper-chromatographic examination indicated the presence of 2-methyl xylose (R_G, 0·39—0·41) and 2 : 3 : 4-trimethyl glucose (R_G, 0·80—0·82; McGilvray, Ph.D. Thesis, Edinburgh, 1949)—pink and brown spots respectively with aniline oxalate. The R_G values of 2: 3 : 4-trimethyl glucose and

2 : 3 : 6-trimethyl glucose are very close, but our spot corresponded more to the former than to the latter. In any case a methoxyl group at $C_{(4)}$ is ruled out by the fact that it was the $C_{(4)}$ carboxyl group which had been converted into the primary alcohol by lithium aluminium hydride.

The amount of 2-methyl xylose and 2 : 3 : 4-trimethyl glucose was also estimated after chromatographic separation by the hypoiodite method and found to be 0·9 : 1 mol. respectively.

Periodate oxidation. The aldobiuronic acid (28 mg.), dissolved in water (10 c.c.), was converted into its sodium salt (by an excess of sodium hydroxide solution and titration of the excess of alkali with acid) and treated with sodium metaperiodate solution (0·28M.; 3 c.c.) and sodium hydrogen carbonate solution (N.; 5 c.c.). The solution was left in the dark and the amount of periodate in the solution was determined (Fleury and Lange, *J. Pharm. Chim.*, 1933, **17**, 107, 196) (Found: 24 hours, 0·7 mol./$C_{15}H_{24}O_{11}$). The oxidised solution was dextrorotatory and gave a positive test for formaldehyde with phenylhydrazine hydrochloride and potassium ferricyanide (Schryver, *Proc. Roy. Soc.*, 1910, *B*, **82**, 226).

The sodium salt of the aldobiuronic acid (21·61 mg. in 15 c.c.) was oxidised for 48 hours with sodium metaperiodate (0·25M.; 5 c.c.), the excess of periodate was destroyed with ethylene glycol (2 c.c.), and the solution titrated with alkali (0·01N.) to methyl-red (Found: 0·05 mole of formic acid per $C_{15}H_{24}O_{11}$ unit).

Fraction (4*a*) reduced Fehling's solution and had $[\alpha]_D^{20}$ +108·5° (*c*, 2·05 in water) (Found: C, 45·7; H, 7·0; OMe, 31·8%; equiv., 395. $C_{15}H_{24}O_{11}$ requires C, 47·1; H, 6·8; OMe, 32·4%; equiv., 382).

Other Experiments.—Viscosity measurement. (1) *Xylan.* The viscosity of a 1·57% solution of the polysaccharide in N-sodium hydroxide solution was determined in an Ostwald viscometer. Mean time of flow of the solution, 693 seconds at 20°; mean time of flow of the alkali at the same temperature, 293 seconds: $\eta_{sp.}/c = 11{\cdot}34$; *c* is expressed in g.-mol. of the repeating units per litre (cf. $\eta_{sp.}/c$ of xylan from esparto grass, 9·8).

(2) *Methylated xylan* (fraction 3, cf. p. 1243). The viscosity of a 1·4% solution of the methylated xylan in *m*-cresol was similarly determined. Mean time of flow (at 20°) of the solution, 852 seconds when the mean time for the solvent was 497 seconds. $\eta_{sp.}/c = 8{\cdot}16$. $M = 6646$ from the Staudinger equation $\eta_{sp.} = K_m Mc$, where $\eta_{sp.}$ = the specific viscosity, K_m = constant, M = molecular weight, and c = concn. in g.-mol. of repeating units per litre (Staudinger and Reinecke, *Annalen*, 1938, **535**, 47; $K_m = 12 \times 10^{-4}$).

A determination of the molecular weight of the methylated xylan (3) by the osmotic-pressure method, through the kindness of Mr. G. Forsyth, gave a value of 17,500 (degree of polymerisation, *ca.* 110).

Periodate oxidation of xylan. (1) *Determination of formic acid liberated.* The method of Halsall, Hirst, and Jones (*J.*, 1947, 1399, 1427), as modified by Chanda, Hirst, Jones, and Percival (*loc. cit.*) for xylan from esparto grass, was used. The formic acid (10^{-3} moles) per $C_5H_8O_4$ units obtained was: 24 hours, 2·20; 72 hours, 3·25; 96 hours, 3·74; 144 hours, 4·51; 240 hours, 5·24; and 336 hours, 5·53. The amount of formic acid liberated was not constant even after 336 hours. A control experiment showed that β-methylxyloside was completely oxidised in 150 hours, and xylan from esparto grass in less than 200 hours.

(2) *Periodate uptake.* The xylan (100 mg.) was shaken in the dark with sodium metaperiodate solution (25 c.c.; 0·25M.), and the amount consumed was determined (Fleury and Lange, *loc. cit.*) at intervals (see Table). A faint trace of xylose could be detected in the hydrolysate of the completely oxidised material (Chanda *et al.*, *loc. cit.*).

Time (hrs.)	24	48	96	144
Mol. of periodate consumed/$C_5H_8O_4$	0·93	0·95	0·98	1·02
$[\alpha]_D$ of the oxidised solution (*c*, 0·4 as wt. of xylan)	+117°	125°	131°	136°

Reducing value of xylan. (1) Hypoiodite oxidation of the polysaccharide in the presence of carbonate–hydrogen carbonate buffer (pH 10·6) gave a value of one reducing group per 42 xylose units.

(2) *Colorimetric method.* Meyer's method (*Helv. Chim. Acta*, 1948, **31**, 103) as applied to xylan from esparto grass (Chanda, Hirst, Jones, and Percival, *loc. cit.*) was used: 62·32 mg. xylan gave $\log I/I_0 = 0{\cdot}095$ corresponding to 90 (xylose curve) or 110—115 (glucose curve) $C_5H_8O_4$ units.

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KING'S BUILDINGS, THE UNIVERSITY OF EDINBURGH. [*Received, January 30th*, 1951.]

277. *Chemical Actions of Ionising Radiations in Solution. Part IX. Radiation Chemistry of Sterols. The Action of X-Rays on (+)-Œstrone-b in Aqueous Solution.*

By Max Keller and Joseph Weiss.

It is shown that the action of *X*-rays on (+)-œstrone-b in aqueous systems leads to formation of a lactone which is identical with that first prepared by Westerfeld (*J. Biol. Chem.*, 1942, **143**, 177). The mechanism of its formation by *X*-rays suggests that the lactone ring is formed by a CO_2H group involving $C_{(17)}$ and an OH group at $C_{(16)}$. Comparison of Westerfeld's lactone with the lactone prepared from œstrone acetate by Jacobsen (*J. Biol. Chem.*, 1947, **171**, 61, 81) has shown that in the pure state they are identical.

In recent investigations we studied the action of *X*-rays on cholesterol, 3β-hydroxypregn-5-en-20-one (Keller and Weiss, *Experientia*, 1950, **6**, 379; *J.*, 1950, 2709), and cholic acid (Keller and Weiss, *J.*, 1951, 25) in aqueous systems. In continuation of this work we now report their action on (+)-œstrone-b, which is of interest since female sex hormones are connected with the incidence of certain forms of malignant growth (cf. Fieser and Fieser, "Natural Products Related to Phenanthrene," New York, 1949, 3rd edn., pp. 330 *et seq.*).

Our first object was again to isolate and to characterise the products of irradiation and consequently we had to employ fairly large doses of *X*-rays (of the order of 10^6 r.). The irradiations were carried out in (i) alkaline and (ii) aqueous acetic acid solutions, with *X*-rays (200 kv.) in the manner described earlier.

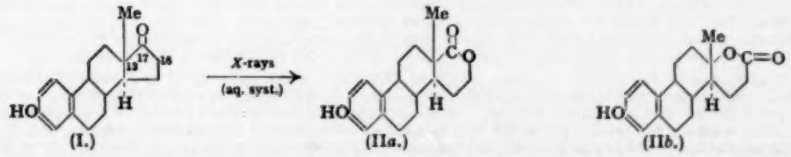
In N-sodium hydroxide 300 mg. of œstrone gave 212 mg. of starting material, 6 mg. of a crystalline compound (A), m. p. 310—312° (decomp.), and 14 mg. of an oil, which were separated chromatographically.

In 90% acetic acid chromatographic separation eventually yielded, from 300 mg. of œstrone, 133 mg. of starting material, 106 mg. of œstrone acetate, 4 mg. of a crystalline compound (B), m. p. 311—313° (decomp.), and 15 mg. of a brown oil.

Compounds (A) and (B), which showed no depression of the melting point when mixed, were in every respect identical. The relatively high melting point, low solubility in organic solvents, and analysis, which corresponded to the formula $C_{18}H_{22}O_3$, suggested that this substance was closely related to one of the lactones obtained by the oxidation of œstrone by hydrogen peroxide (Westerfeld, *J. Biol. Chem.*, 1942, **143**, 177) or by the oxidation of œstrone acetate by Jacobsen's method (*J. Biol. Chem.*, 1947, **171**, 61, 81). Although the melting points given for these lactones were somewhat higher (334—339°), Mather (quoted by Smith, *Endocrinology*, 1944, **35**, 146; *Proc. Soc. Exp. Biol. Med.*, 1945, **59**, 242) who repeated Westerfeld's procedure gives m. p. 309° for the lactone. As the relation between these two chemically prepared lactones was not clear and in order to compare them with the product obtained by the irradiation, we prepared these compounds and purified them carefully. We found that the lactone, prepared according to either Westerfeld or Jacobsen melted at 310—312° (decomp.) (Kofler block), and there was no depression of the melting point on mixing them or their acetates, and the optical rotations were ($[\alpha]_D^{21}$ +39·8° ± 4°, in pyridine). These lactones are thus identical. Identity with the compound obtained by the irradiation was proved by analysis and mixed melting point.

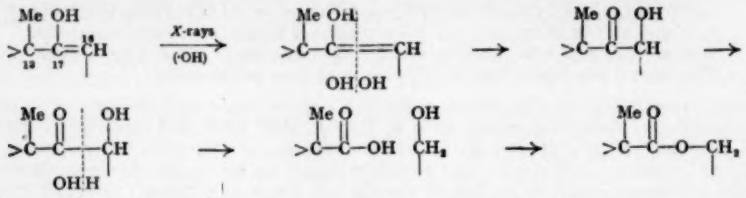
This lactone is interesting since Smith (*loc. cit.*) has shown that it stimulates the release of luteinizing hormone from the pituitaries of immature female rats, eliciting this response in smaller doses than does œstrone.

The formation of the œstrone lactone (II*a* or II*b*) from œstrone (I) corresponds to the net process:



Formulæ (II*a*) and (II*b*) were suggested by Jacobsen and Westerfeld respectively. There is no *definite* evidence at present to decide between these two structures but the character of the

CO_2H obtained by " hydrolysis " is evidence on the lactone structure in general. However, some conclusions can be drawn from the fact that the lactone is also formed by the action of *X*-rays. It is now fully established that ionising radiations produce hydrogen atoms and hydroxyl radicals in their action on water (Weiss, *Nature*, 1944, **153**, 748; *Trans. Faraday Soc.*, 1947, **43**, 314) and it is known from the previous work on steroids (Keller and Weiss, *loc. cit.*) that under the conditions in question double bonds are easily attacked by the hydroxyl radicals and can also be split under suitable conditions. In the five-membered ring of œstrone (I) a double bond can be only created between $C_{(14)}$ and $C_{(17)}$ (by enolisation of the carbonyl group at $C_{(17)}$, fission of which leads to structure (II*a*), as shown by the following scheme :



If one accepts this mechanism, structure (II*b*) is excluded as the tertiary character of $C_{(13)}$ does not allow the formation of a 13 : 17-double bond.

Experimental.

All m. p.s taken on the Kofler block (±2°).

Action of X-*Rays on* (+)-*Œstrone-b in Alkaline Solution.*—Œstrone (300 mg.; m. p. 258—260°), dissolved in N-sodium hydroxide (60 ml.), was irradiated with *X*-rays (200 kv.; *ca.* 3×10^6 r.) at 30—35°. The solution was then acidified (Congo-red), and the precipitate centrifuged, washed with water, dried in a desiccator, and treated with 50-ml. portions of ether, whereafter a colourless powder (P_1) remained (42 mg.). The ethereal extract was dried and the ether removed. The residue (240 mg.) was chromatographed through alumina (6 g.; standardised according to Brockmann). The column was prepared in benzene and the substance suspended in the latter. The column was eluted with 20-ml. portions of solvents. Benzene–ether (4 : 1 ⟶ 3 : 2) gave unchanged œstrone (200 mg.), m. p. 258—260° (from alcohol) not depressed by admixture with an authentic specimen. Chloroform gave a crystalline material (4 mg.), small prisms (1·2 mg.) (from alcohol), m. p. 311—312° (decomp.), darkening from 307°. The m. p. of this substance was not depressed on admixture with Westerfeld's lactone (*loc. cit.*) or with Jacobsen's lactone (*loc. cit.*). Further elution with chloroform–methanol (19 : 1) gave a brown oil (14 mg.). The powder (P_1) (42 mg.) was repeatedly recrystallised from alcohol, and the small prisms thus obtained (4·5 mg.) had m. p. 310—312° (decomp.), becoming brown from 307°, not depressed on admixture with Westerfeld's or Jacobsen's lactone. For analysis the compound was dried in a vacuum over phosphoric oxide at 130° (Found : C, 75·8; H, 7·9. Calc. for $C_{18}H_{22}O_3$: C, 75·5; H, 7·74%). The mother-liquor was chromatographed through alumina (1 g.), which was prepared as above. Benzene–ether (4 : 1) gave œstrone (12 mg.), m. p. 258—260° (from alcohol) not depressed on admixture with an authentic specimen. Elution with chloroform gave again a very small amount of the lactone, m. p. 310—312°, not depressed on admixture as above. Elution with chloroform–methanol (19 : 1) gave small amounts of an uncrystallisable brown oil.

Action of X-*Rays on* (+)-*Œstrone-b in Aqueous Acetic Acid.*—Œstrone (300 mg.; m. p. 258—260°) in 90% acetic acid (300 ml.) was irradiated with *X*-rays (*ca.* 3×10^6 r.) at 30—35°. The solvent was then removed in a vacuum at 35° and the oily residue extracted with ether. The ether-insoluble residue (9 mg.), after recrystallisation from alcohol, yielded small prisms (3·6 mg.), m. p. 310—312° (decomp.), not depressed on admixture with Westerfeld's or Jacobsen's lactone. The ethereal extract was washed with water, then dried (Na_2SO_4), and the ether removed. The oily residue (273 mg.) was chromatographed through alumina (8 g.), standardised according to Brockmann. Elution with light petroleum–benzene (1 : 1) in which the column was also prepared gave œstrone acetate (86 mg.), m. p. 125—126° (from methanol) not depressed on admixture with an authentic specimen. Elution with benzene gave crystals (~35 mg.) which were shown to be a mixture of œstrone acetate (~20 mg.) and œstrone (~10 mg.). Elution with benzene–ether gave unchanged œstrone (123 mg.), m. p. 258—260° (from alcohol) not depressed on admixture with an authentic specimen. Elution with chloroform gave small amounts of the lactone, m. p. 311—313° (from alcohol) not depressed on admixture with Westerfeld's lactone. Elution with chloroform–methanol (19 : 1) gave a non-crystallisable brown oil (15 mg.).

Preparation of Westerfeld's Lactone.—Œstrone (300 mg.; m. p. 258—260°) in N-sodium hydroxide (60 ml.) was treated with hydrogen peroxide (10%) (3·8 ml.), and the reaction allowed to proceed at room temperature and in the dark for 3 days. Subsequently the solution was acidified, and the precipitate collected, washed with water, and dried in a desiccator. The residue was extracted 8 times with 25-ml. portions of ether. The remaining residue, repeatedly recrystallised from alcohol, gave small prisms, m. p. 310—312° (decomp.), becoming brown from 307° (62 mg.); the mixed m. p. with Jacobsen's lactone was 310—313°. For analysis it was dried for 6 hours over phosphoric oxide in a vacuum at 130° (Found : C, 75·2; H, 7·8%). $[\alpha]_D^{21}$ was +39·8° ± 4° (*c*, 1·108 in pyridine).

The lactone (20 mg.) in pyridine (1 ml.) and acetic anhydride (0·5 ml.) was set aside for 48 hours at room temperature. The solvent was then evaporated in a vacuum, the residue dissolved in ether, washed until neutral, and dried (Na_2SO_4), and the ether removed. Recrystallisation from methanol gave diamond-shaped crystals (14 mg.), m. p. 147—149° not depressed on admixture with the lactone acetate prepared according to Jacobsen's method (*loc. cit.*).

Preparation of Jacobsen's Lactone.—To œstrone acetate (300 mg.; m. p. 125—126°) in acetic acid (3 ml.) was added hydrogen peroxide (32·5%; 2 ml.), and the solution was kept in the dark at 35° for 72 hours. The reaction mixture was then diluted with water until crystals appeared. After collection and drying, the crystals had m. p. 146—150° (205 mg.). Recrystallised from methanol, they had m. p. 148—150°, not depressed on admixture with Westerfeld's lactone acetate.

This acetate (140 mg.), dissolved in methanol (4 ml.), was treated with potassium hydroxide (1 ml.; 10%) and refluxed for 1½ hours. Subsequently 10 ml. of water were added and the methanol was removed in a vacuum. The precipitate formed on acidification (hydrochloric acid) was centrifuged, washed with water, and dried in a desiccator. Repeated crystallisation from alcohol gave small prisms (90 mg.), m. p. 311—313° (decomp.), not depressed on admixture with Westerfeld's lactone, and having $[\alpha]_D^{21}$ +39·4° ± 4° (*c*, 0·762 in pyridine).

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UNIVERSITY OF DURHAM, KING'S COLLEGE,
NEWCASTLE-ON-TYNE, 1.

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278. *The Distribution of the Lower Fatty Acids between Water and a Variety of Solvents.*

By MANSEL DAVIES, PERCY JONES, D. PATNAIK, and E. A. MOELWYN-HUGHES.

The distribution of acetic acid and of propionic acid between water and a variety of relatively immiscible solvents has been examined experimentally at various concentrations and temperatures.

The increase in internal energy attending the dissociation of the double molecules, which is 14·5 kcals. in the vapour phase, is about 9 in typical un-ionising media such as benzene, *n*-hexane, and light petroleum, and about 6 in ionising solvents such as chloroform, chlorobenzene, and nitrobenzene.

The results for the two acids in the eight solvents used are consistent with the view that the force of attraction between the constituents of the dimers is principally if not entirely electrostatic.

WHEN a monobasic acid ionises to an extent, α, in water, and forms double molecules in a second solvent, s, with which the aqueous solution is in equilibrium, the total concentrations, C_w and C_s, in the water and in the second solvent are related to each other as follows:

$$C_s/[C_w(1-\alpha)] = K_1 + 2K_1^2C_w(1-\alpha)/K_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where K_1 and K_2 are the equilibrium constants governing, respectively, the transfer of un-ionised monomeric molecules from the aqueous layer to the other solvent [HA (water) $\rightleftarrows$ HA (solvent)], and the dissociation of the dimer in the non-aqueous layer [$(HA)_2 \rightleftarrows 2HA$]. In two earlier treatments of this distribution problem (Hendrixson, *Z. anorg. Chem.*, 1897, **13**, 73; Moelwyn-Hughes, *J.*, 1940, 850), the factors 2 and α, respectively, were omitted.

Equation (1) satisfactorily accounts for the distribution of acetic acid between (*a*) water and (*b*) *n*-hexane, benzene, carbon tetrachloride, carbon disulphide, chlorobenzene, and nitrobenzene, and of propionic acid between (*a*) water and (*b*) light petroleum (b. p. 110—120°), carbon tetrachloride, benzene, chloroform, chlorobenzene, and nitrobenzene. The range of concentration used was such that the highest aqueous concentration was about N. The acids were purified by crystallisation, and the solvents by fractional distillation after appropriate treatment, *e.g.*, with mercuric sulphate in the case of carbon disulphide, dilute sodium hydroxide solution in the case of chlorobenzene, alkaline permanganate in the case of hexane, and phosphoric oxide in the case of nitrobenzene. The experimental method did not differ significantly from the conventional. Values of α were calculated from known ionisation constants (Harned and Ehlers, *J. Amer. Chem. Soc.*, 1933, **55**, 652, 1379; Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, 1943). The units in which K_2, the entropy *S*, and the heat content *H* are given in Tables I and II are, respectively, g.-mol. per l., cals. per g.-mol. °K., and kcals. per g.-mol. We accept 14·49 kcals. as the most reliable value of ΔH_2 for acetic acid in the vapour phase (Ritter and Simons, *J. Amer. Chem. Soc.*, 1945, **67**, 757; cf. 14·57 found for acetic acid by Fenton and Garner, *J.*, 1930, 694, 14·03 ± 0·20 found

for acetic acid by Johnson and Nash, *J. Amer. Chem. Soc.*, 1950, **72**, 547, and 14·125 given for formic acid by Coolidge, *ibid.*, 1928, **50**, 2166). Compared with this value, those of 16·4 for acetic acid (McDougall, *ibid.*, 1936, **58**, 2585) and of 18·5 ± 2 for propionic acid (*idem*, *ibid.*, 1941, **63**, 3420) appear to be high. The equilibrium constants for the two gaseous dimerisations given

TABLE I.

Acetic acid.

Solvent.	Temp. (° K.)	10^3K_1. Obs.	10^3K_1. Calc.	10^3K_2. Obs.	10^3K_2. Calc.	$\Delta S°_1$.	ΔH_1.	$\Delta S°_2$.	ΔH_2.
None	308·10	—	—	0·072	—	—	—	28·09	14·49
n-C_6H_{14} ...	298·15	1·43	1·445	1·17	1·170	3·40	4·89±0·25	16·70	8·98±0·54
	308·15	1·89	1·892	1·925	1·926	—	—	—	—
	318·15	2·425	2·426	3·05	3·044	—	—	—	—
C_6H_6	298·15	8·9	8·75	7·68	7·67	3·91	3·97±0·16	17·79	8·19±0·68*
	308·15	10·9	10·86	12·40	12·04	—	—	—	—
	318·15	13·2	13·34	18·27	18·31	—	—	—	—
CCl_4	298·15	3·55	3·549	2·07	2·066	2·17	3·99±0·29	13·07	7·56±0·74
	308·15	4·38	4·417	3·11	3·134	—	—	—	—
	318·15	5·42	5·421	4·60	4·605	—	—	—	—
CS_2	290·1	1·49	1·491	1·38	1·370	2·64	4·52±0·23	11·20	7·05±0·43
	300·1	1·95	1·930	2·02	2·054	—	—	—	—
	310·1	2·47	2·469	3·06	3·017	—	—	—	—
C_6H_5Cl ...	298·15	7·50	7·49	7·08	7·06	−0·55	2·74±0·24	7·00	5·02±0·34
	308·15	8·70	8·72	9·39	9·37	—	—	—	—
	318·15	10·03	10·04	12·06	12·10	—	—	—	—
$C_6H_5{\cdot}NO_2$	298·15	36·1	36·1	136	136	4·94	3·44±0·11	7·20	5·25±0·42
	308·15	43·7	43·7	180	182	—	—	—	—
	318·15	52·0	52·2	238	237	—	—	—	—

* Cf. 9·70 (*J.*, 1940, 850). A repetition of the distribution between benzene and water, carried out after communication of this paper, gave 8·80±0·2.

TABLE II.

Propionic acid.

Solvent.	Temp. (°K.).	10^3K_1. Obs.	10^3K_1. Calc.	10^3K_2. Obs.	10^3K_2. Calc.	$\Delta S°_1$.	ΔH_1.	$\Delta S°_2$.	ΔH_2.
None	308·10	—	—	0·034	—	—	—	—	—
Light	293·2	7·03	7·02	7·41	9·29	6·692	4·855±0·040	17·62	9·37±0·06
petroleum	303·2	9·23	9·23	12·53	12·53	—	—	—	—
	313·2	11·90	11·91	20·56	20·56	—	—	—	—
	323·2	15·16	15·17	32·80	32·81	—	—	—	—
CCl_4	293·2	16·0	16·0	1·25	1·25	5·222	3·940±0·20	12·06	7·43±0·25
	303·2	20·1	20·0	1·93	1·91	—	—	—	—
	313·2	24·6	24·6	2·81	2·83	—	—	—	—
C_6H_6	293·2	42·8	42·9	6·17	5·96	7·16	3·935±0·125	16·25	7·75±0·56
	303·2	53·8	53·6	9·26	9·30	—	—	—	—
	313·2	65·8	65·9	13·7	13·94	—	—	—	—
	323·2	80·2	80·2	20·8	20·52	—	—	—	—
$CHCl_3$	293·2	162	162·5	29·8	29·7	5·49	2·67±0·14	15·72	6·66±0·12
	303·2	190	188·8	43·1	43·3	—	—	—	—
	313·2	218	217·7	61·6	61·5	—	—	—	—
	323·2	247	248·2	85·4	85·7	—	—	—	—
C_6H_5Cl	293·2	367	368·0	5·79	5·75	8·70	3·135±0·16	11·19	6·29±0·21
	303·2	441	438·3	8·56	8·19	—	—	—	—
	313·2	516	517·4	11·4	11·44	—	—	—	—
	323·2	607	606·4	15·7	15·64	—	—	—	—
$C_6H_5{\cdot}NO_2$	298·2	159	161·4	150	151·0	5·76	2·80±0·21	15·92	5·87±0·57
	323·2	234	232·7	317	324·4	—	—	—	—
	350·4	328	325·6	681	660·9	—	—	—	—

in Table III have been obtained from the published values after extrapolation and conversion of units. The dielectric constants D, and the characteristic reciprocal temperatures, $L = \frac{1}{D}\left(\frac{dD}{dT}\right)_p$, given in Table III, have been reproduced from Moelwyn-Hughes, "Kinetics of Reactions in Solution," 2nd. edn., Oxford, 1947, p. 91, with the exception of the data for carbon

disulphide, for which L based on Landolt–Börnstein's " Tabellen " is found to be $8{\cdot}99 \times 10^{-4}$ degree^{-1}.

Because the aqueous solutions to which these results refer are saturated with the organic solvent, and the organic solvent is saturated with water, neither the heat of transfer, ΔH_1, nor the heat of dissociation, ΔH_2, refers to pure media. Nevertheless, a determination of ΔH_2 for

TABLE III.

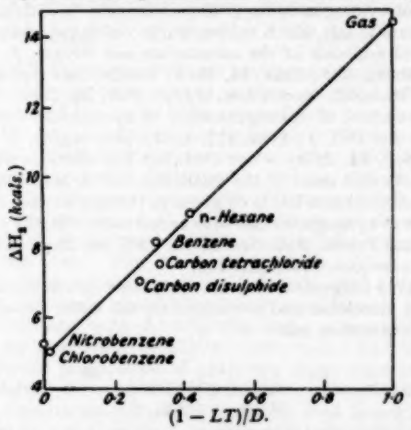
The dissociation of the double molecules of acetic acid and propionic acid in various media at 308·1° K.

Medium.	10^3K_2.	K_2 relative for acetic acid.	10^3K_2 for propionic acid.	$\frac{K_2 \text{ (acetic)}}{K_2 \text{ (propionic)}}$	D.	$(1 - LT)/D$.
Vapour	0·072	1	0·034	2·1	—	—
n-C_6H_{14}	1·93	27	1·61	1·2	1·87	0·41
CCl_4	3·11	43	2·25	1·4	2·22	0·33
C_6H_6	12·4	172	11·4	1·1	2·25	0·32
CS_2	2·80	39	—	—	2·60	0·275
$CHCl_3$	—	—	51·5	—	4·31	−0·014
C_6H_5Cl	9·39	130	9·67	1·0	6·37	+0·014
$C_6H_5{\cdot}NO_2$.....	180	2,500	208	0·9	33·1	−0·020

benzoic acid in pure benzene by a vapour-pressure method (Wall and Rouse, *J. Amer. Chem. Soc.*, 1941, **63**, 3002) gave a value $9{\cdot}0 \pm 0{\cdot}4$, in substantial agreement with the value 8·7 found by distribution experiments (Hendrixson, *loc. cit.*). The presence of water in the organic layer does not, in this case, affect the heat of dimerisation.

It would be inappropriate on such incomplete evidence as we here present to discuss in detail the effect of the solvent on the hydrogen bridge (Latimer and Rodebush, *J. Amer. Chem. Soc.*, 1920, **42**, 1419)—a subject which has been extensively reviewed (Lasettre, *Chem. Reviews*, 1937,

Heats of dissociation of dimeric acetic acid in various media.



20, 259; Mansel Davies, *Ann. Reports*, 1946, **43**, 5). Moreover, our data are only accurate enough to indicate the sign, but not the magnitude of $d(\Delta H_2)/dT$. The general trend of the heat and extent of dimerisation with the dielectric constant of the solvent, however, justifies brief comment.

If the dipole moment of a dissolved molecule is not affected by dissolution (see Onsager, *J. Amer. Chem. Soc.*, 1936, **58**, 1486; Kirkwood, *J. Chem. Physics*, 1939, **7**, 911), and if the force of attraction, though not necessarily that of repulsion, between the two molecules is electrostatic, then the increase in free energy ΔG_2, attending the dissociation of the dimer in solution, is given either by the expression :

$$\Delta G_2 = \Delta G_g/D \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

or by the expression

$$\Delta G_2 = (D + 2)\Delta G_g/3D \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2a)$$

where the subscript g refers to the vapour phase. ΔG_g may be calculated in terms of the configuration and polarity of the two molecules forming the complex (Moelwyn-Hughes, *J.*, 1938, 1243). By applying the Gibbs–Helmholtz equation, the increase in heat content is

$$\Delta H_s = [(1 - LT)/D]\Delta H_g \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

or

$$\Delta H_s = \{[D + 2(1 - LT)]/3D\}\Delta H_g \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3a)$$

The first of these relations is shown in the Figure. Because the coefficient of ΔH_g in equation 3*a* is equal to a constant plus a constant fraction of its coefficient in equation 3, a plot of ΔH_s against $[(D + 2(1 - LT)]/3D$ must also be nearly linear, though passing near to or through the origin. These results show that such information as we have on the influence of the solvent on the dimerisation of monocarboxylic acids is not inconsistent with electrostatic principles, as far as these can at present be applied to the complicated system of solutions of polar molecules.

THE EDWARD DAVIES CHEMICAL LABORATORIES,
UNIVERSITY COLLEGE OF WALES, ABERYSTWYTH.
THE DEPARTMENT OF PHYSICAL CHEMISTRY,
THE UNIVERSITY, CAMBRIDGE.

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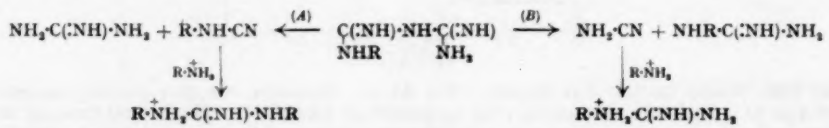
279. *Amidines. Part XV. Preparation of Diguanides and Guanidines from Cyanoguanidine and Ammonium Sulphonates.*

By P. OXLEY and W. F. SHORT.

A number of diguanides and guanidines have been prepared by fusion of cyanoguanidine with ammonium sulphonates. The mechanism of the reaction is discussed.

CONSIDERABLE experimental evidence is available in support of the view that the formation of guanidine by fusion of cyanoguanidine (" dicyandiamide ") with ammonium salts involves the production of a diguanide salt which subsequently yields two molecules of a guanidine salt by reaction with a second molecule of the ammonium salt (Davis, *J. Amer. Chem. Soc.*, 1921, **43**, 2234; Blair and Braham, *ibid.*, 1922, **44**, 2346; Smith, Sabetta, and Steinbach, *Ind. Eng. Chem.*, 1931, **23**, 1124; Mannelli, *Ann. Chim. Appl.*, 1933, **23**, 235). The production of some guanidine by depolymerisation of cyanoguanidine to cyanamide which then reacts with an ammonium salt (Werner and Bell, *J.*, 1920, **117**, 1133; also Sugino, *J. Chem. Soc. Japan*, 1939, **60**, 351; *Chem. Abs.*, 1940, **34**, 2273) is not excluded but there is no direct evidence for the participation of cyanamide and most of the guanidine salt is undoubtedly produced from the diguanide salt. Much less attention has been given to the preparation of substituted diguanides and guanidines by fusion of cyanoguanidine with amine salts (Smolka and Friedreich, *Monatsh.*, 1888, **9**, 230; Lumière and Perrin, *Bull. Soc. chim.*, 1905, **33**, 205; Slotta and Tschesche, *Ber.*, 1929, **62**, 1400; Bobeck, *Annalen*, 1931, **487**, 295).

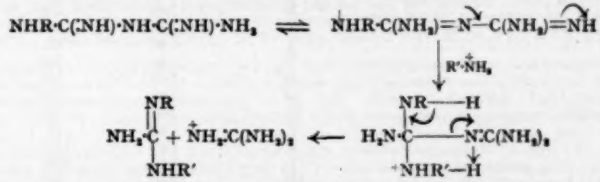
Sugino (*loc. cit.*, p. 411) suggested that the diguanide produced in the first stage of this reaction decomposes to a guanidine and a cyanamide, the latter subsequently being converted into a guanidine by the ammonium salt:



Fission of the diguanide is analogous to the decomposition of a hemi-acetal:

and the proportion of the diguanide decomposed in the alternative directions (*A* and *B*) can be correlated with the basic strength of the resulting guanidines. We have observed in several cases that the decomposition of diguanide salts is facilitated by the presence of a base, indicating

that the diguanide is more readily decomposed than its salts. Thus, *iso*propyldiguanide toluene-*p*-sulphonate and *m*-chloroaniline afforded guanidine and *iso*propylguanidine at a temperature at which the diguanide salt is stable in absence of chloroaniline. Moreover, we find that cyanoguanidine and sulphanilamide toluene-*p*-sulphonate afford *p*-sulphonamidophenyldiguanide (44%), whereas the use of free sulphanilamide leads to the production of sulphanilylguanidine (Buttle, Dewing, Foster, Gray, Smith, and Stephenson, *Biochem. J.*, 1938, **32**, 1101; Dewing and Smith, *Nature*, 1941, **148**, 24; White, Bratton, Litchfield, and Marshall, *J. Pharmacol.*, 1941, **72**, 113). No diguanide was obtained from cyanoguanidine and 2-aminopyridinium toluene-*p*-sulphonate, owing presumably to acceleration of its decomposition by the second basic centre in the molecule. Although diguanide salts decompose at higher temperatures in the same way as the free bases, the only evidence for the production of a substituted cyanamide during the preparation of guanidines from cyanoguanidine and substituted ammonium salts is Sugino's observation that a condensation product of phenylcyanamide and cyanamide, probably 6-amino-2 : 4-dianilino-1 : 3 : 5-triazine, is formed as by-product when N^1-phenyldiguanide is heated with ammonium chloride. Cooper, Partridge, and Short (*J.*, 1950, 395) advanced reasons for the view that decomposition of diamidides to amidines by ammonium salts involves a 1 : 4-addition, and the production of guanidines from diguanides may well follow a parallel course. The relative activity of the different conjugated systems in the diguanide and the direction in which the addition complexes decompose will be controlled by the substituents and will determine the proportions in which the different substituted guanidines are formed. The following selected example is given to illustrate the general scheme :



The nature of the anion in the ammonium salt has a considerable influence on the yield of diguanide and guanidine obtained from cyanoguanidine, an effect which may sometimes be attributed mainly to lowering of the fusion temperature (Ewan and Young, *J. Soc. Chem. Ind.*, 1921, **40**, 109T; Sugino, *loc. cit.*). For example, diguanide is obtained in 21—23% yield when ammonium chloride is used (Bamberger and Dieckmann, *Ber.*, 1892, **25**, 545), whereas a 45% yield is obtained with ammonium iodide (Ostrogovich, *Bul. Soc. Stiinte Bucuresti*, 1910, **19**, 641; *Chem. Abs.*, 1911, **5**, 2102). Ammonium thiocyanate (Werner and Bell, *loc. cit.*) and ammonium nitrate (Sprengstoffwerke in Spandau, G.P. 222,522; Davis, *J. Amer. Chem. Soc.*, 1921, **43**, 669, 2234; Blair and Braham, *ibid.*, 1922, **44**, 2342) are especially effective in the preparation of guanidine from cyanoguanidine. We have prepared a number of diguanides from cyanoguanidine and ammonium sulphonates (1 mol.) at 140—160° and the results are collected in Table II. The yields, although reproducible, vary considerably with the N^1-substituent, the best results being obtained with N^1-aryldiguanides. Cyanoguanidine and ammonium sulphonates (2 mols.) at *ca.* 200° afford guanidine sulphonates, and the use of sulphonates is specially advantageous in the preparation of guanidine itself, since it is obtained practically free from the amorphous by-products (ammelide, ammeline, melamine) with which it is invariably contaminated when the ammonium salt of an inorganic acid is employed. Alkylguanidines are conveniently prepared in the same way, an alkylammonium sulphonate being used. The method is less satisfactory for the preparation of arylguanidines, since fission of the diguanide in the alternative direction (cf. *A*, above) is then appreciable and the *N*-arylguanidine is contaminated with an N^1N^3-diarylguanidine, $HN{:}C(NHAr)_2$, and with guanidine, so that the yield is poor.

Experimental.*

Preparation of Ammonium Sulphonates.—The ammonium salts recorded in Table I were prepared from equivalent quantities of their constituents.

Preparation of Diguanides.—An equimolecular mixture of cyanoguanidine and the ammonium sulphonate (usually 0·01—0·05 g.-mol.) was heated in a vapour-bath, with occasional stirring, to the

* See also B.P. 593,675, 610,379.

TABLE I.

Amine salts.

Amine.	Salt.†	Solvent for crystn.	Form.	M. p.	Formula.	Analyses. Found, N, %.	Reqd., N, %.
(1) Diethylamine ...	T	$COMe_2$	Flat needles	103°	$C_{11}H_{19}O_3NS$	5·7	5·7
(2) Piperidine	T	$COMe_2$	Flat needles	126	$C_{12}H_{19}O_3NS$	5·4	5·45
(3) *cyclo*Hexylamine	T	Pr^iOH	Flat needles	184	$C_{13}H_{21}O_3NS$	5·1	5·2
(4) Benzylamine ...	T	Pr^iOH	Rect. plates	185·5	$C_{14}H_{17}O_3NS$	5·05	5·0
(5) Methylaniline ...	B	Pr^iOH–Et_2O	Plates	82—83	$C_{13}H_{15}O_3NS$	5·3	5·3
(6) Sulphanilamide	B	MeOH	Prisms	255 (decomp.)	$C_{21}H_{16}O_5N_2S_2$	8·5	8·5
(7) Diphenylamine	T	C_6H_6	Flat needles	134·5	$C_{18}H_{15}O_3NS$	4·2	4·1

† B = benzenesulphonate; T = toluene-*p*-sulphonate.

(1) Norton and Otten (*Amer. Chem. J.*, 1888, **10**, 140) record m. p. 88°.
(4) Noller and Liang (*J. Amer. Chem. Soc.*, 1932, **54**, 670) record m. p. 184·5—185·5°.
(7) Norton and Otten (*loc. cit.*) state that diphenylammonium toluene-*p*-sulphonate has m. p. 64°.

TABLE II.

Synthesis of Diguanides.

N^1-Substituent(s) in diguanide.	Ammonium sulphonate.*	Reaction temp.	Reaction time (mins.).	Yield, %.
(1) None	B	140°	60	30
(2) ,, ...	M	140	60	18
(3) Me	B	160	20	37
(4) Pr^i	T	160	90	79
(5) *cyclo*Hexyl	T	140	60	36
(6) CH_2Ph	T	140	30	78
(7) Ph	B	160	15	75
(8) ,, ...	M	140	15	96
(9) p-$C_6H_4{\cdot}SO_2{\cdot}NH_2$	B	160	20	44
(10) Me_2	T	160	10	75
(11) Et_2	T	140	120	39
(12) $-[CH_2]_5-$	T	140	120	62
(13) Me, Ph	B	140	40	95
(14) Ph_2	T	140	30	73

N^1-Substituent(s) in diguanide.	Toluene-*p*-sulphonate. M. p.	Formula.	Found, N, %.	Reqd., N, %.	Picrate. M. p.	Formula.	Found, N, %.	Reqd., N, %.
(1) None	232—233° †	$C_9H_{13}O_3N_5S$	25·8	25·6	238° †	$C_9H_{10}O_7N_8$	33·9	33·9
(2) ,, ...	—	—	—	—	—	—	—	—
(3) Me	—	—	—	—	—	—	—	—
(4) Pr^i	161—161·5	$C_{12}H_{21}O_3N_5S$	22·4	22·2	165·5	$C_{11}H_{16}O_7N_8$	30·1	30·1
(5) *cyclo*Hexyl	158	$C_{13}H_{23}O_3N_5S$	19·7	19·7	158·5	$C_{14}H_{20}O_7N_8$	27·5	27·2
(6) CH_2Ph	142—143	$C_{16}H_{21}O_3N_5S$	18·7	19·3	150	$C_{15}H_{16}O_7N_8$	26·5	26·7
(7) Ph	—	—	—	—	184	$C_{14}H_{14}O_7N_8$	27·6	27·6
(8) ,, ...	—	—	—	—	—	—	—	—
(9) p-$C_6H_4{\cdot}SO_2{\cdot}NH_2$	—	—	—	—	—	—	—	—
(10) Me_2	150	$C_{11}H_{19}O_3N_5S$	23·3	23·3	—	—	—	—
(11) Et_2	142	$C_{13}H_{23}O_3N_5S$	21·2	21·3	147	$C_{13}H_{18}O_7N_8$	29·0	29·0
(12) $-[CH_2]_5-$	177	$C_{14}H_{23}O_3N_5S$	20·3	20·5	178	$C_{13}H_{18}O_7N_8$	28·2	28·1
(13) Me, Ph	—	—	—	—	169·5	$C_{15}H_{14}O_7N_8$	26·6	26·7
(14) Ph_2	210·5	$C_{21}H_{23}O_3N_5S$	16·5	16·5	—	—	—	—

* B = Benzenesulphonate; M = methanesulphonate; T = toluene-*p*-sulphonate.
† With decomp.

(1) The yields were 29 and 28% after ¾ and 1½ hours respectively. (3) N^1-*Methyldiguanide benzenesulphonate* separated from *iso*propanol in plates, m. p. 146° (Found: N, 25·6. $C_9H_{13}O_3N_5S$ requires N, 25·6%). The form of methylguanidine benzenesulphonate having m. p. 138·5° (see below) was also isolated from the reaction product in 43% yield. (7) N^1-Phenyldiguanide had m. p. 145—146°. Cohn (*J. pr. Chem.*, 1911, **84**, 396) states that the base and the picrate have m. p. 144—146° and 176—179°, respectively. N^1-*Phenyldiguanide benzenesulphonate* crystallised from ethanol in prisms, m. p. 181° (Found: N, 20·9. $C_{14}H_{17}O_3N_5S$ requires N, 20·9%). (8) N^1-*Phenyldiguanide methanesulphonate* separated from ethanol in prisms, m. p. 198—199° (decomp.) (Found: C, 39·8; H, 5·7. $C_9H_{15}O_3N_5S$ requires C, 39·6; H, 5·5%). (9) N^1-p-*Sulphonamidophenyldiguanide benzenesulphonate* crystallised from water in plates, m. p. 205—206° (decomp.) (Found: N, 20·2. $C_{14}H_{18}O_5N_6S_2$ requires N, 20·3%). (12) The toluene-*p*-sulphonate separated from water as a *monohydrate* (Found: Loss at 100°, 5·2, 5·0. $C_{14}H_{23}O_3N_5S,H_2O$ requires H_2O, 5·0%). (13) N^1-*Methyl*-N^1-*phenyldiguanide benzenesulphonate* crystallised from *iso*propanol in prisms, m. p. 147·5° (Found: N, 20·2. $C_{15}H_{19}O_3N_5S$ requires N, 20·1%).

temperature recorded in Table II. The mixture usually melted completely and there was an exothermic reaction which raised the internal temperature 5—15° above that of the bath for a few minutes. The mixture sometimes solidified immediately (Nos. 7, 8, 9, 14) or on cooling (Nos. 4, 10, 13), and the resulting diguanide sulphonate could usually be isolated by crystallisation from water or alcohol. In cases where the salt was both readily soluble and obtained in low yield, the reaction product was dissolved in water and precipitated with an excess of aqueous copper toluene-*p*-sulphonate and ammonia; the resulting very sparingly soluble, pink, crystalline copper toluene-*p*-sulphonate complexes were suspended in hot water and decomposed with hydrogen sulphide. The copper sulphide was removed and the filtrate was concentrated to obtain the diguanide toluene-*p*-sulphonate. The diguanide picrates were obtained from the sulphonates and ammonium or lithium picrate solution and were purified by crystallisation from water.

Preparation of Guanidines.—Guanidine. (1) Cyanoguanidine (2 g.) and ammonium benzenesulphonate (10 g., 2·3 mols.) were heated at 260° for ½ hour, and the cold product was crystallised from water, giving guanidine benzenesulphonate, m. p. 211° (9·8 g., 95%). Karrer and Epprecht (*Helv. Chim. Acta*, 1941, **24**, 311) record m. p. 212°. (2) When a mixture of cyanoguanidine (8·4 g.) and ammonium benzenesulphonate (17·5 g., 1 mol.) was heated in a bath at 160°, the internal temperature rose in 10 minutes to 190°, and then fell again. The mixture was heated for an hour in all and then crystallised from water, giving guanidine benzenesulphonate, m. p. 210—211° (19·8 g., or 88% based on the ammonium salt). (3) Cyanoguanidine (4·2 g.) and ammonium phenol-*p*-sulphonate (20 g., 2·05 mols.) were heated at 200° for 1½ hours and then crystallised from *iso*propanol. *Guanidine phenol*-p-*sulphonate*, m. p. 201—201·5° (Found: N, 18·2. $C_7H_{11}O_4N_3S$ requires N, 18·0%), was obtained in 92% yield (21·5 g.). (4) Cyanoguanidine (4·2 g.) and ammonium toluene-*p*-sulphonate (20 g., 2·1 mols.) afforded guanidine toluene-*p*-sulphonate, m. p. 231—231·5° (22·4 g., 97%), when heated at 210° for ½ hour and then at 225° for ½ hour. The pure salt was obtained when the reaction product was crystallised from water (Found: N, 18·3. Calc. for $C_8H_{13}O_3N_3S$: N, 18·2%). Remsen and Garner (*Amer. Chem. J.*, 1901, **25**, 185) give m. p. 206° for this salt; Perrot (*Bull. Soc. chim.*, 1946, **13**, 557) records m. p. 230°. (5) *Guanidine methanesulphonate* was obtained in 90% yield when cyanoguanidine (42 g.) and ammonium methanesulphonate (120 g., 2·1 mols.) were heated at 210° for ½ hour; after crystallisation from methanol, the salt had m. p. 207° (Found: N, 27·0. Calc. for $C_2H_9O_3N_3S$: N, 27·1%). Perrot (*loc. cit.*) records m. p. 206—207°.

N-Methylguanidine. Cyanoguanidine (4·2 g.) and methylammonium benzenesulphonate (21 g., 2·2 mols.) were heated at 210° for 25 minutes, and the cooled product was crystallised from *iso*propanol, giving *N-methylguanidine benzenesulphonate*, m. p. 128° (Found: N, 18·2. $C_8H_{11}O_3N_3S$ requires N, 18·2%). A second *form* of the benzenesulphonate, crystallising from *iso*propanol in long needles, m. p. 138·5° (Found: C, 41·7; H, 5·6; N, 18·3. $C_8H_{11}O_3N_3S$ requires C, 41·6; H, 5·7; N, 18·2%), was obtained from cyanoguanidine and methylammonium benzenesulphonate (1 mol.) at 160° (Table II). A mixture of the two forms melted sharply at 128°. The benzenesulphonate, m. p. 138·5°, afforded a pale yellow picrate, crystallising in long, slender, flat needles, m. p. 202°, apparently identical with the α-picrate described by Lecher (*Annalen*, 1927, **455**, 156, 164). The picrate prepared from the benzenesulphonate, m. p. 128°, also had m. p. 202° but crystallised in dark orange rods which appeared to be identical with Lecher's β-form.

NN-Dimethylguanidine. A mixture of cyanoguanidine (2·1 g.) and dimethylammonium toluene-*p*-sulphonate (11·5 g., 2·1 mols.) was kept at 200° for 1 hour and then crystallised from *iso*propanol, giving *NN-dimethylguanidine toluene*-p-*sulphonate* (8·1 g., 60%), m. p. 179° (Found: N, 16·4. $C_{10}H_{17}O_3N_3S$ requires N, 16·2%).

*N-iso*Propylguanidine. (1) The product obtained by heating cyanoguanidine (2·1 g.) and *iso*propylammonium toluene-*p*-sulphonate (11·55 g., 2·1 mols.) at 200° for 2 hours was dissolved in warm *iso*propanol (25 c.c.). The solution deposited guanidine toluene-*p*-sulphonate (2·0 g.), m. p. and mixed m. p. 231°, and the residue obtained by evaporating the filtrate to dryness was crystallised from water, giving *isopropylguanidine toluene*-p-*sulphonate* (6·3 g., 46%), m. p. 120° (Found: C, 47·3; H, 6·9; N, 15·7. $C_{11}H_{19}O_3N_3S$ requires C, 48·4; H, 7·0; N, 15·4%). (2) A mixture of *N*¹-*iso*propyldiguanide toluene-*p*-sulphonate (2·1 g.) and *m*-chloroaniline (0·85 g.) afforded guanidine toluene-*p*-sulphonate (0·32 g., 21%), m. p. 231°, and *N-iso*propylguanidine toluene-*p*-sulphonate (1·22 g., 67%), m. p. 115—118°, after being heated at 160° for 16 hours. There was no reaction when *N*¹-*iso*propyldiguanide toluene-*p*-sulphonate and *iso*propylammonium toluene-*p*-sulphonate (1 mol.) were heated at 160° for 2 hours.

*N-cyclo*Hexylguanidine. (1) The product obtained by heating cyanoguanidine (4·2 g.) and *cyclo*hexylammonium toluene-*p*-sulphonate (13·55 g., 1 mol.) at 200° for 1 hour gave guanidine toluene-*p*-sulphonate (3 g.), m. p. 231°, on crystallisation from *iso*propanol. The solid obtained by diluting the filtrate with ether was crystallised from water or acetone and afforded colourless plates of N-*cyclohexylguanidine toluene*-p-*sulphonate* (4·6, 26%) m. p. 136—136·5° (Found: N, 13·6. $C_{14}H_{23}O_3N_3S$ requires N, 13·4%). The *picrate* separated from water in needles, m. p. 230° (Found: N, 22·75. $C_{19}H_{18}O_7N_6$ requires N, 22·7%). (2) A mixture of cyanoguanidine (2·1 g.) and *cyclo*hexylammonium toluene-*p*-sulphonate (13·55 g., 2 mols.) similarly gave 0·9 g. and 3·3 g. of the toluene-*p*-sulphonates of guanidine and *N-cyclo*hexylguanidine, respectively.

N-Phenylguanidine. A mixture of cyanoguanidine (4·2 g.) and phenylammonium benzenesulphonate (12·55 g., 1·0 mol.) was heated at 200° for an hour, and then digested with water (100 c.c.) at 100° until the insoluble gum solidified. The mixture was cooled, the crude *NN'*-diphenylguanidine benzenesulphonate (2·6 g.) was collected, the filtrate was evaporated to dryness, and the residue was extracted with acetone, leaving guanidine benzenesulphonate (4·8 g., 44%), m. p. and mixed m. p. 212°. The solid obtained by evaporating the acetone solution was crystallised from a little water and gave rectangular prisms of *N-phenylguanidine benzenesulphonate*, m. p. 155° (Found: N, 14·6. $C_{13}H_{13}O_3N_3S$ requires

N, 14·7%). The picrate crystallised from water in long needles, m. p. 227·5° (Found: N, 23·2. Calc. for $C_{18}H_{18}O_7N_6$: N, 23·1%). Kämpf (*Ber.*, 1904, **37**, 1682) records m. p. 221—222°. The crude *NN'*-diphenylguanidine benzenesulphonate was converted into the *picrate*, m. p. 171° (Found: N, 19·3. $C_{18}H_{14}O_7N_6$ requires N, 19·1%), and the *nitrate*, m. p. *ca.* 190° (decomp.) (Found: N, 20·7. $C_{13}H_{14}O_3N_4$ requires N, 20·4%)

RESEARCH LABORATORIES, MESSRS. BOOTS PURE DRUG CO. LTD.,
NOTTINGHAM.
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280. *The Electrolytic Dissociation of Metal Hydroxides.*

By C. W. DAVIES.

The hydroxides of most metals are weaker electrolytes in water than their other compounds, and it is suggested that this is due to the absence of the hydration shell which normally protects the metal cation. As a result, the metal hydroxides may appear to be abnormally weak, either because of true covalent bonding or, in other cases, simply on account of small ionic size. A criterion for the occurrence of covalent forces in this class of compound is suggested.

A GENERAL understanding of the dissociation constants found for "strong" electrolytes is complicated by lack of a quantitative theory of ionic hydration. For instance, the association of magnesium, calcium, strontium, and barium with the nitrate or iodate ion increases, like the ionic mobility, with the atomic number, but with certain other anions the order is reversed, and incomplete dissociation is most evident with magnesium. The difference can, rather crudely, be explained by supposing that in the first case ion-pair formation does not involve the penetration of the hydration shell of the cation by the anion (the association thus being purely electrostatic) whereas in the second case it does (thus introducing the possibility of true co-ordinative bonding), but clearly a satisfactory treatment of electrolytic dissociation will require more detailed knowledge of the hydration energies of ions.

The metal hydroxides are particularly interesting in this respect. Although dilute salt solutions are frequently supposed, in the absence of information to the contrary, to be completely dissociated, yet it is common knowledge that most common salts, except those of sodium, potassium, calcium, and barium, show marked hydrolysis; the hydroxides of most metals are therefore much weaker electrolytes than their other compounds. There is no obvious property of the hydroxide ion, such as extreme polarisability or very small size, which would put it in quite a different category from other anions, and yet this apparent anomaly in the modern theory of solutions has received little attention.

A possible explanation is that with the hydroxides alone there is no likelihood of the cation being separated from its associated ion by water molecules. Thus for most anions the configuration M^+, H_2O, X^- may represent the closest approach of the metal ion to the anion X in aqueous solution; but for the hydroxides this configuration M^+, H_2O, OH^- would tend to pass over into M^+, OH^-, H_2O, and so the protective effect of ionic hydration is lost.

It is true that Harned (cf. Harned and Owen, "Physical Chemistry of Electrolytic Solutions," Reinhold, 2nd edn., 1950, p. 385) has suggested a formulation: $M^+ \ldots OH^- \ldots H^+ \ldots OH^-$, with the proton regarded as oscillating between the hydroxyl groups, to account for the mean activity coefficients of the alkali-metal hydroxides; but even if such a complex were formed, its primary dissociation would be much more likely to give rise to $M^+ \ldots OH^- + H_2O$ than to $M^+, H_2O + OH^-$.

The first three columns of the following table give a selection of the more reliable data at

Metal.	*K*.	Ref.	*b* (Pauling).	*a* (Bjerrum).	Metal.	*K*.	Ref.	*b* (Pauling).	*a* (Bjerrum).
Li	1·2	a	2·00	2·35	La ...	$\sim 5 \times 10^{-4}$	f	2·55	~1·6
Na ...	(5)	a, b	2·35	3·31	Ag ...	0·005	g	2·66	<1
K	strong	a	2·73	>3·52	Tl^I ...	0·38	b	2·55	1·2
					Zn ...	4×10^{-5}	h, j	2·14	<1
Mg ...	0·0026	c	2·05	1·3	Cu^{II} ...	$3·4 \times 10^{-7}$	h	2·22	<1
Ca ...	0·050	b, d	2·39	2·45					
Ba ...	0·23	b, e	2·75	5·55					

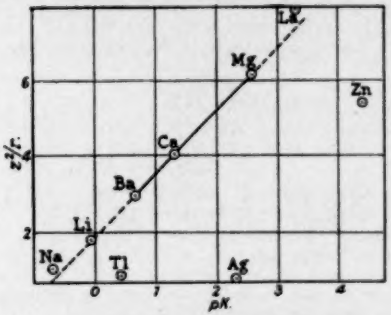
(a) Darken and Meirs, *J. Amer. Chem. Soc.*, 1942, **64**, 622 (conductivity). (b) Bell and Prue, *J.*, 1949, 362 (kinetic). (c) Stock and Davies, *Trans. Faraday Soc.*, 1948, **44**, 856 (potentiometric). (d) Davies and Hoyle, *J.*, 1950, (solubility). (e) Davies, *J.*, 1939, 349 (potentiometric). (f) Estimated from Kolthoff and Elmquist's pH measurements (*J. Amer. Chem. Soc.*, 1931, **53**, 1217). (g) J. Bjerrum, *Chem. Rev.*, 1950, **46**, 384 (potentiometric). (h) Calculated from Owen and Gurry's pH measurements (*J. Amer. Chem. Soc.*, 1938, **60**, 3074). (j) Kolthoff and Kameda, *ibid.*, 1931, **53**, 832 (potentiometric).

present available for the dissociation constants of metal hydroxides. The K values are thermodynamic constants for the process $(M, OH)^{(n-1)+} \rightleftharpoons M^{n+} + OH^-$.

That of sodium hydroxide is so high as to be subject to considerable experimental uncertainty, but nevertheless the same value has been reached independently by two entirely different methods. Col. 4 of the table shows the sum of the crystallographic radii (in A.) of the cation and the oxygen ion; a mean value of 1·40 is taken for the latter (Pauling, "Nature of the Chemical Bond," 2nd edn., Cornell Univ. Press, p. 346; Bernal and Megaw, *Proc. Roy. Soc.*, 1935, *A*, **151**, 388). Both for the alkali and the alkaline-earth metals, the strength of the hydroxide increases with the interionic distance, in agreement with the view that the radius of the bare cation is the governing factor.

If the complication of ionic hydration is absent with hydroxides, this group of electrolytes should be especially favourable for testing Bjerrum's theory of ion association (*Kgl. Danske Vid. Selsk., Mat.-fys. Medd.*, 1926, **7**, No. 9) which yields, for cases where the interaction is purely electrostatic, a relation between the dissociation constant of an ion pair and the closest distance of approach of the participating ions.

Values calculated for the latter quantity are given in cols. 5 and 10 of the table. Comparison with the figures in the preceding column shows that there are large differences between the calculated values and the crystallographic data. The Bjerrum value for $MgOH^+$ is too small whilst that for $BaOH^+$ is impossibly large, and systematic deviations of the same kind, though less pronounced, are evident in the data for the alkali metals. Of course Bjerrum's theory was



intended as a simplified, and not as an exact, treatment of the problem; for instance, the normal dielectric constant of water is used in calculating the Coulomb interaction between two ions in contact. Bell and Prue (*loc. cit.*) have cited the impossibly low Bjerrum value for thallous hydroxide as evidence that an electrostatic explanation is inadequate, and that covalent forces must be involved in the formation of the undissociated molecule; but the table shows that this test is of doubtful value and might lead to false conclusions when applied, for instance, to lanthanum or magnesium.

It should nevertheless be possible to find an experimental criterion for the occurrence of covalent forces. If we assume that these are absent among the alkali and alkaline-earth metals, we have a limited body of data in which K should be a function only of ionic size (and valency). In the Figure, the negative logarithms of the K values collected in the table are plotted against z^2/r, where z is the valency of the cation and r its radius (Pauling, *op. cit.*). The points for the alkaline-earth metals fall accurately on a straight line, so that with this one valency group, where the relationship between radius and pK can be tested, it seems to be fully upheld. The empirical valency factor is more doubtful, but within the present limits of experimental error the points for Li, Na, and La are quite consistent with the same straight line, which may therefore serve as a useful criterion of ion-pair formation due wholly to electrostatic forces.

The equation of the line is $pK = 0{\cdot}607z/r^2 - 1{\cdot}150$, and if our criterion is correct this equation should express the behaviour of ideally strong metal hydroxides. Any deviations, such as those shown by zinc, copper, thallium, and silver, should be in the direction of lower dissociation constants, and the size of the deviation should indicate the extent to which covalent forces contribute in the formation of the hydroxide. The conclusion that specific chemical forces are involved with the metals named is supported by other arguments. These and other transitional metals form numerous co-ordination compounds, and their cations probably form

definite chemical hydrates (cf. J. Bjerrum, *loc. cit.*); their formation of hydroxy-compounds is best written as

$$M,(H_2O)_n] + H_2O \rightleftharpoons [MOH,(H_2O)_{n-1}] + H_3O^+$$

If the ionic radius of beryllium is inserted in our equation the corresponding dissociation constant is 2×10^{-7}. The dissociation constant of beryllium hydroxide is not known, but it is interesting to see that the relationship now put forward would account for a very marked hydrolysis of beryllium salts without recourse to other explanations. The application to aluminium is more doubtful owing to the importance of the valency factor. The correctness of the valency-square relationship being assumed, the calculated dissociation constant of $AlOH^{++} \rightleftharpoons Al^{+++} + OH^-$ would be 2×10^{-10}, so that again the very weak basic constant appears as a logical outcome of the high valency and small ionic radius of the metal, and the hydroxy-compound may be 100% ionised, though only very slightly dissociated.

EDWARD DAVIES CHEMICAL LABORATORIES,
ABERYSTWYTH, WALES.

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281. *Cyanamides. Part V.* N-*Aryl*-N′-*arylsulphonylureas.*

By FREDERICK KURZER.

N-Aryl-*N*′-arylsulphonylureas, R′·NH·CO·NH·SO_2R, have been prepared by two methods, and some aspects of their chemical behaviour have been examined.

INTERACTION of arylureas and aromatic sulphonyl chlorides has recently been shown to occur with simultaneous dehydration to yield *N*-aryl-*N*-arylsulphonylcyanamides R′·SO_2·NR·CN (Part I, *J.*, 1949, 1034). This probably involves the intermediate formation of the highly unstable *iso*urea sulphonates of the type R′·SO_2·O·C(:NH)·NHR (Oxley, Partridge, Peak, and Short, *Chem. and Ind.*, 1949, 419; Kurzer, *ibid.*, p. 522), several observations having provided indirect evidence in support (Parts III and IV, *J.*, 1949, 3033; 1950, 3269). An alternative mechanism, *viz.*, the intermediate formation of *N*-aryl-*N*′-arylsulphonylureas, followed by dehydration and rearrangement if necessary, had been tentatively considered (cf. Part I, *loc. cit.*); it was pointed out at the same time, however, that such compounds, synthesised by independent methods, were not dehydrated under the conditions of the urea–sulphonyl chloride reaction, and all subsequent observations have supported the mechanism involving *iso*urea sulphonates. Some new observations on the synthesis and properties of *N*-aryl-*N*′-arylsulphonylureas are now recorded.

Before 1940 only two methods for the preparation of sulphonylureas had been reported. Cleve (*Ber.*, 1888, **21**, 3266, 3273) had obtained two apparently impure sulphonylurea derivatives by the action of potassium cyanate on sulphonamides of the naphthalene series, and Billeter (*Ber.*, 1904, **37**, 690) synthesised several benzenesulphonylureas by interaction of amines with the difficultly accessible benzenesulphonyl *iso*cyanate. During recent years interest in certain substituted sulphonylureas was aroused because of their close structural relation to chemotherapeutically valuable sulphonamides. Thus, *p*-aminobenzenesulphonylurea and related compounds were prepared by suitable variations of the numerous conventional urea syntheses (see references 3—9, Table 1).

The only two routes explored for the preparation of *N*-aryl-*N*′-arylsulphonylureas are Billeter's method which afforded *N*-benzenesulphonyl-*N*′-phenylurea (equation 1, p. 1259), and the interaction of a sulphonamide with an aryl *iso*cyanate (Haak, U.S.P. 2,385,571; Geigy, B.P. 538,884) (equation 2).

In the present investigation three possible methods of preparing such urea derivatives were examined. Interaction of sulphonamides and arylureas in alkaline media (equation 3) gave *N*-phenyl-*N*′-toluene-*p*-sulphonylurea and the *N*-*p*-methoxyphenyl analogue, but not the corresponding benzenesulphonylphenylurea. Although various conditions were employed, the yield did not exceed 10—15%. A further disadvantage was the necessity of removing unchanged sulphonamide and *s*-diarylurea, formed as by-product during the prolonged heating.

More favourable results were obtained in the interaction of aromatic sulphonamides and *iso*cyanates (equation 2). Haak (*loc. cit.*) had condensed the reactants in the absence of solvents, and Geigy (*loc. cit.*) had used nitrobenzene as medium. Preliminary experiments in various

solvents gave moderate yields, which were greatly improved by the presence of triethylamine. Thus, in anhydrous toluene 25—30% yields of the sulphonylurea were obtained, and *s*-diphenylurea was formed as by-product; the addition of triethylamine, particularly in relatively large quantities (approximately 0·25 mole), accelerated the condensation considerably and gave up to 90% yields. The use of tertiary amines for catalysing the reaction between *iso*cyanates and hydroxyl-containing compounds is well known (Tarbell, Mallat, and Wilson, *J. Amer. Chem. Soc.*, 1942, **64**, 2229) and has recently been studied in detail by Baker and Gaunt (*J.*, 1949, 9). The interaction of *iso*cyanates and amines, on the other hand, proceeds normally so readily that no attempts to employ tertiary amines as catalysts appear to be on record (cf. Saunders and Slocombe, *Chem. Reviews*, 1948, **43**, 203). It may be pointed out that in the latter reaction the amine may be responsible for autocatalytic effects. When replaced, in the present reaction, by a sulphonamide, of essentially acidic character, the addition of a tertiary base becomes significant. The difference in the velocity with which amino- and sulphonamido-groups react with *iso*cyanic esters is clearly illustrated by Roth and Degering's observation (*J. Amer. Chem. Soc.*, 1945, **67**, 126) that approximately equimolecular proportions of *p*-aminobenzenesulphonamide and *iso*cyanates react to form *N*-aryl-*N'*-*p*-sulphonamidophenylureas: the *iso*cyanate is consumed preferentially by the primary amino-group of the molecule, and the sulphonamido-grouping remains unaffected. Analogous results have also been obtained in the thiourea series (Dyson, B.P. 517, 682).

$$R'\cdot SO_2\cdot NCO + R\cdot NH_2 \longrightarrow R'\cdot SO_2\cdot NH\cdot CO\cdot NHR \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$R'\cdot SO_2\cdot NH_2 + R\cdot NCO \longrightarrow R'\cdot SO_2\cdot NH\cdot CO\cdot NHR \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$R'\cdot SO_2\cdot NH_2 + R\cdot NH\cdot CO\cdot NH_2 \longrightarrow R'\cdot SO_2\cdot NH\cdot CO\cdot NHR + NH_3 \quad . \quad . \quad . \quad (3)$$

$$R'\cdot SO_2Cl + R\cdot NH\cdot CO\cdot NH_2 \longrightarrow R'\cdot SO_2\cdot NH\cdot CO\cdot NHR + HCl \quad . \quad . \quad . \quad (4)$$

It has been claimed (Geigy, B.P. 538,884; U.S.P. 2,371,178; Swiss P., 224,070) that melting *p*-nitrobenzenesulphonyl chloride with urea, first at 100—120° and later at 140°, gave *p*-nitrobenzenesulphonylurea (equation 4). However, the constants quoted for this compound, and for the *p*-amino-derivative obtained therefrom by reduction, are anomalous (see Table). Remsen and Garner (*Amer. Chem. J.*, 1901, **25**, 175) have shown that aromatic sulphonyl chlorides and urea at *ca.* 100° yield sulphonates of amidinourea, $NH_2\cdot CO\cdot NH\cdot C(:NH)\cdot NH_2$. Repetition of Remsen's work, under Geigy's conditions, gave no evidence of sulphonylurea formation.

In this connexion the behaviour of an aromatic urea on fusion with a sulphonyl chloride was also examined. Phenylurea and toluene-*p*-sulphonyl chloride formed a homogeneous melt and interacted slowly at 100°, yielding toluene-*p*-sulphonanilide. Above 140—150°, vigorous evolution of hydrogen chloride occurred, but decomposition resulted, producing the sulphonanilide, ammonium toluene-*p*-sulphonate, and *s*-diphenylurea. Since a blank experiment established that *N*-phenyl-*N*-toluene-*p*-sulphonylcyanamide does not yield toluene-*p*-sulphonanilide on prolonged fusion with toluene-*p*-sulphonyl chloride—although it does afford the latter product in acid media under certain conditions (cf. Part II, *J.*, 1949, 3029)—the sulphonylcyanamide does not appear to be an intermediate in the arylurea–sulphonyl chloride fusion. The reaction products are therefore probably formed directly by the union of the sulphonyl chloride with the decomposition products of the aromatic urea.

A second synthesis of sulphonylureas and sulphonylthioureas from sulphonyl halides and substituted ureas, using a modified Schotten–Baumann technique, has been claimed (Migliardi and Tappi, *Arch. Sci. biol.*, 1941, **27**, 164). Here again the results were not confirmed and have been discussed elsewhere (Leitch *et al.*, *Canad. J. Res.*, 1945, **23**, *B*, 139; Kurzer, *J. Appl. Chem.*, 1951, **1**, 80).

Method.	$NO_2\cdot C_6H_4\cdot SO_2\cdot NH\cdot CO\cdot NH_2$. M. p.	$NH_2\cdot C_6H_4\cdot SO_2\cdot NH\cdot CO\cdot NH_2$. M. p.
I. $R\cdot SO_2Cl + NH_2\cdot CO\cdot NH_2$ ...	190° (decomp.) [1]	320° (subl.) [1]; 303° (decomp.) [2];
II. $R\cdot SO_2\cdot NH_2 + H\cdot NCO$	—	149—154° [3]; 158—160° [4];
III. $R\cdot SO_2\cdot NH\cdot CN + H\cdot OH$	178—180° [5]	143—147° [6]; 140° [7];
IV. $R\cdot SO_2Cl + NH_2\cdot C(OMe):NH$ [8]	—	140° [9]; 140—146° [9]

[1] Geigy, *loc. cit.* [2] Migliardi and Tappi, *loc. cit.* [3] Haak, *loc. cit.* [4] Martin *et al.*, U.S.P. 2,411,661. [5] Backer and Moed, *Rec. Trav. chim.*, 1947, **66**, 335. [6] Leitch *et al.*, *loc. cit.* [7] Winnek *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 1682. [8] Followed by hydrolysis. [9] Cox, *ibid.*, p. 2225; see also Haak, G.P. 741,533.

The persistent failure of urea and its *N*-substituted derivatives to afford *N*-sulphonylureas by interaction with sulphonyl chlorides (equation 4) under all conditions so far examined is in marked contrast to the behaviour of *O*-substituted ureas, which yield *N*-sulphonyl derivatives

without difficulty (Cox and Raymond, *J. Amer. Chem. Soc.*, 1941, **63**, 300) (equation 5). This is accounted for satisfactorily if sulphonyl halides will be substituted at the nitrogen atom only if the enolic hydroxyl group is already effectively blocked by a substituent. In the absence of such substituents the formation of highly unstable intermediate *O*-sulphonyl*iso*ureas, R·NH·C(O·SO_2R′):NH, may be assumed. Their immediate decomposition to cyanamides and arylsulphonic acids, followed by further changes, explains the production of amidinourea from urea (cf. Oxley, Partridge, Peak, and Short, *loc. cit.*) and of sulphonylcyanamides from *N*-arylureas (this series, Parts II—IV, *locc. cit.*). Intermediate *O*-sulphonyl esters cannot, of course, arise from *O*-substituted *iso*ureas, which react therefore simply to yield *N*-sulphonyl-*iso*ureas (equation 5) in aqueous media in the presence of sodium hydroxide, *i.e.*, under conditions where ureas fail to react at all.

$$R'\cdot SO_2Cl + NH_2\cdot C(OMe){:}NH \longrightarrow R'\cdot SO_2\cdot NH\cdot C(OMe){:}NH \quad . \quad . \quad . \quad . \quad (5)$$

Sulphonylureas decompose on melting. Arylsulphonylureas, for example, resolidified immediately after melting and then decomposed at a higher temperature. Backer and Moed (*Rec. Trav. chim.*, 1947, **66**, 689; *Bull. Soc. chim. Belg.*, 1948, **57**, 211) have shown that certain *p*-nitroarylsulphonyl-guanidines and -ureas decomposed in alkaline media, and sometimes on prolonged fusion, with elimination of sulphur dioxide (equation 6). It has now been found that, in general, sulphonylureas decompose fairly rapidly above their melting points to yield the corresponding sulphonamide and *iso*cyanate (equation 7):

$$NO_2\cdot C_6H_4\cdot SO_2\cdot NH\cdot C(:NPh)\cdot NHPh \longrightarrow NO_2\cdot C_6H_4\cdot NH\cdot C(:NPh)\cdot NHPh + SO_2 \quad . \quad (6)$$

$$R'\cdot SO_2\cdot NH\cdot CO\cdot NHR \longrightarrow R'\cdot SO_2\cdot NH_2 + R\cdot NCO \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Toluene-*p*-sulphonylurea, for example, when kept above 220° for 30 minutes decomposed completely to yield toluene-*p*-sulphonamide and cyanuric acid (probably by polymerisation of the intermediate *iso*cyanic acid). The formation of cyanuric acid accounts for the resolidification, after fusion, of arylsulphonylureas and for the resumed decomposition at higher temperatures. Urea derivatives bearing substituents on both nitrogen atoms decomposed analogously: *N*-phenyl-*N*′-toluene-*p*-sulphonylurea evolved phenyl *iso*cyanate and gave a residue of the sulphonamide and small quantities of *s*-diphenylurea.

The action of certain dehydrating agents on *N*-aryl-*N*′-arylsulphonylureas has also been examined. Thionyl chloride, phosphorus oxychloride, and toluene-*p*-sulphonyl chloride, which are generally employed in the conversion of amides into nitriles, failed to remove the elements of water from sulphonylureas under the conditions used. Under restrained conditions (*e.g.*, short action of thionyl chloride at room temperature; heating with toluene-*p*-sulphonyl chloride in pyridine) the sulphonylurea was unaffected while more vigorous action resulted in fission: *N*-phenyl-*N*′-toluene-*p*-sulphonylurea, for example, gave toluene-*p*-sulphonyl chloride and aniline on brief boiling with phosphorus oxychloride. Heating the sulphonylurea with thionyl chloride or phosphorus oxychloride in pyridine gave intractable oils. These results show that *N*-aryl-*N*′-arylsulphonylureas do not undergo dehydration under the conditions of the synthesis of *N*-aryl-*N*-arylsulphonylcyanamides from aromatic ureas (cf. Part I, *loc. cit.*). Their intermediate formation in the latter reaction is therefore ruled out, which provides further indirect support for the alternative mechanism involving *O*-sulphonylureas.

Experimental.

M. p.s are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford.

*N-Phenyl-N′-toluene-*p*-sulphonylurea.*—(a) *From phenylurea.* A solution of toluene-*p*-sulphonamide (17·1 g., 0·1 mol.), phenylurea (15 g.; 0·11 mol.), and sodium carbonate (7·2 g., 0·14 equiv.) in water (180 ml.) was refluxed for 12 hours. A white crystalline deposit collected gradually in the condenser, ammonia was slowly given off, and small quantities (2—4 g.) of *s*-diphenylurea appeared in suspension and were quickly filtered off with suction when refluxing was complete. The filtrate was diluted with water (300 ml.), made strongly alkaline with sodium hydroxide solution (20% w/w; 50 ml.), and cooled; a small deposit of unchanged phenylurea (1—2 g.; m. p. 145—148°) separating overnight was removed by filtration. On acidification of the filtrate to Congo-red with concentrated hydrochloric acid (50 ml.) in the cold, unchanged toluene-*p*-sulphonamide and the reaction product were precipitated. When the mechanically stirred mixture was slowly heated to 95°, the former product dissolved; the crude sulphonylurea was quickly filtered off (filtrate A) and washed by twice heating it nearly to boiling with water (2 × 100 ml.). Crystallisation of the dried material (4—5 g.; m. p. 169—173°) by dissolution in acetone (10 ml.)–benzene (30 ml.), treatment with charcoal, and addition of light petroleum (b. p. 60—80°; 35 ml.) gave white needles of *N-phenyl-N′-toluene-*p*-sulphonylurea*, m. p. 172—174° (3—4 g., 10—14%) (Found: C, 57·95; H, 5·0. $C_{14}H_{14}O_3N_2S$ requires C, 57·9; H, 4·8%), soluble in acetone, ethanol, benzene, or sodium hydroxide solution, sparingly soluble in light petroleum or chloroform, and

insoluble in water. From filtrate A, unchanged toluene-*p*-sulphonamide (10 g., 60%) separated overnight.

When the sodium carbonate was substituted by equivalent quantities of sodium or potassium hydroxide, or when the time of reaction was prolonged, no significant increases of the yields were observed. Addition of various proportions of ethanol to the solvent did not accelerate the reaction, nor were yields improved.

The method failed to afford *N*-benzenesulphonyl-*N*′-phenylurea from benzenesulphonamide and phenylurea in alkaline media.

(b) *From phenyl isocyanate*. To a suspension of toluene-*p*-sulphonamide (43 g., 0·25 mol.) in phenyl *iso*cyanate (40 g., 0·33 mol.), triethylamine (6 ml.) was added and the mixture, the temperature of which rose spontaneously, was heated on the steam-bath for 6 hours. The orange-yellow viscous liquid, which began to solidify after 3 hours and set to a hard crystalline mass on cooling, was broken into lumps while still warm, powdered, and dissolved by stirring with successive portions of sodium hydroxide solution at 60° (total 1200 ml.; 4% w/w). The residual insoluble white powder was filtered off and gave, after further extraction with alkali (200 ml.; 4% w/w) and washing with hot water, small quantities of *s*-diphenylurea, m. p. 242° (6—8 g.). The combined alkaline extracts were stirred with charcoal at 30° for 15 minutes and filtered. The clear colourless filtrate was cooled to 0° and slowly added with stirring to excess of ice-cold acetic acid (1 l.; 30%), the crude sulphonylurea separating as a white flocculent precipitate. (Precipitation by the addition of acid to the alkaline liquid at room temperature yielded a yellow oil that solidified slowly and was purified with difficulty.) After being set aside at 0° for several hours, the material was filtered off, washed with water (dry wt., 60—65 g., 83—90%; m. p. 152—156°) and crystallised from ethanol–water (120 ml. and 40 ml. respectively), giving colourless, glass-like, large needles (32—35 g., 44—48%) of *N*-phenyl-*N*′-toluene-*p*-sulphonylurea, m. p. 172—174° (Found: C, 58·0; H, 4·9%). It was difficult to isolate further pure material from the sticky filtrate, which tended to yield oils. After removal of the solvent, further small quantities (6—10 g.) of the product, m. p. 170—171°, could be obtained by reprecipitation from alkaline solution as described above. [N.B. Material purified by two reprecipitations instead of crystallisation, although having a lower m. p. (160—164°), gave excellent analytical results (C, 57·9; H, 4·9%) and was suitable for use in further experiments.]

Interaction of the reagents in toluene (1 l.) for 20 hours, in the absence of the tertiary base as catalyst, gave 25—30% yields. (See also below, N-benzenesulphonyl-*N*′-phenylurea).

N-*Benzenesulphonyl*-N′-*phenylurea*.—A solution of benzenesulphonamide (15·7 g., 0·1 mol.) and phenyl *iso*cyanate (35·7 g., 0·3 mol.) in anhydrous toluene (400 ml.) was refluxed for 18 hours. After removal of the solvent on the steam-bath under reduced pressure, the viscous oily residue was twice extracted with hot sodium hydroxide solution (2 × 250 ml.; 4% w/w), the granular *s*-diphenylurea (8 g.) filtered with suction, and the cooled filtrate slowly added to excess of ice-cold acetic acid, the product separating as a white precipitate (18·5 g.; m. p. 164—166°). Crystallisation from ethanol–water (30 : 20 ml.) gave *N*-benzenesulphonyl-*N*′-phenylurea (9·2 g., 33%), m. p. 166—167°, in small needles (Found: C, 56·75; H, 4·5. Calc. for $C_{13}H_{12}O_3N_2S$: C, 56·5; H, 4·35%). Base-catalysed interaction of the reactants in the absence of solvent (as described for *N*-phenyl-*N*′-toluene-*p*-sulphonylurea) gave improved yields (60—70%).

N-p-*Methoxyphenyl*-N′-*toluene*-p-*sulphonylurea*.—A hot solution of toluene-*p*-sulphonamide (8·6 g., 0·05 mol.) and *p*-methoxyphenylurea (10·0 g., 0·06 mol.) in ethanol (40 ml.)–water (40 ml.) was treated with sodium carbonate (5·3 g., 0·1 equiv.) in water (60 ml.) and refluxed for 15 hours. After removal of most of the ethanol by distillation and addition of sodium hydroxide solution (100 ml.; 5% w/w), the purple liquid deposited unchanged *p*-methoxyphenylurea (5 g.) on cooling. The filtrate was made acid to Congo-red with concentrated hydrochloric acid. On dilution to 200 ml. and heating to 80°, the unchanged toluene-*p*-sulphonamide (4·3 g., 50%) dissolved and was quickly decanted from the purple oil, which gave, on repeated crystallisation from benzene–light petroleum and finally benzene, large elongated lustrous prisms of N-p-*methoxyphenyl*-N′-*toluene*-p-*sulphonylurea*, initially separating with benzene of crystallisation and having an indefinite m. p. (Yield, 2·2 g., 15%) (Found: C, 63·8; H, 5·2. $C_{15}H_{16}O_4N_2S,C_6H_6$ requires C, 63·3; H, 5·5%). Short drying at 80—100° yielded the compound as a microcrystalline powder, m. p. 160—162° (Found: C, 56·1; H, 5·3; N, 9·0; S, 9·75. $C_{15}H_{16}O_4N_2S$ requires C, 56·25; H, 5·0; N, 8·75; S, 10·0%).

Toluene-p-*sulphonylurea* (cf. Haak, U.S.P. 2,385,571).—A solution of toluene-*p*-sulphonamide (57 g., 0·33 mol.) in ethanol, to which sodium cyanate (32 g., 0·5 mol.) dissolved in water (100 ml.) was added, was boiled under reflux for 8 hours. The suspended cyanate dissolved gradually (3—4 hours). After removal of about two-thirds of the ethanol in a vacuum, the residual solution was diluted with water (400 ml.) and filtered, and deposited overnight small quantities of the starting material. The filtrate therefrom gave, on acidification with acetic acid, a white precipitate (48 g., 68%) of toluene-*p*-sulphonylurea. Crystallisation from boiling water (80 ml. per g.) gave minute lustrous needles, m. p. 200—202° (followed by rapid resolidification; subsequent decomposition at >320°) (Found: N, 12·8. Calc. for $C_8H_{10}O_3N_2S$: N, 13·1%). Haak (*loc. cit.*) gives m. p. 184—188°.

Thermal Decomposition of Toluene-p-*sulphonylurea*.—Toluene-*p*-sulphonylurea (10·7 g., 0·05 mol.) was inserted in a metal-bath at 230°. After fusing completely within a few minutes, the material began to resolidify to a yellowish-white paste while slight loss of *iso*cyanic acid occurred. Heating at 220—210° was continued for ½ hour, the cooled product boiled with three successive portions of ethanol (25, 12, and 12 ml.), and the residual white powder filtered off (filtrate A). The residue (1·6 g., 75%) was recrystallised from boiling water (40 ml.), giving prismatic crystals of cyanuric acid [Found: C, 28·2; H, 2·5; N, 33·0; *M* (volumetrically; cf. Hantzsch, *Ber.*, 1906, **39**, 139), 132, 136. Calc. for $C_3H_3O_3N_3$: C, 27·9; H, 2·3; N, 32·6%; *M*, 129]. It was identified by conversion into the *p*-nitrobenzyl derivative,

m. p. 278° (Found : N, 21·4. Calc. for $C_{18}H_8O_4N_4$: N, 21·2%), the m. p. being undepressed on admixture with a specimen prepared from authentic cyanuric acid (cf. Lyons and Reid, *J. Amer. Chem. Soc.*, 1917, **39**, 1727).

The ethanolic filtrates (A) were evaporated to smaller volume (20 ml.) and filtered from a further trace of granular solid, and then deposited toluene-*p*-sulphonamide, m. p. 136—137° (undepressed by authentic material) (total, 7·2 g., 84%).

Thermal Decomposition of N-*Phenyl*-N'-*toluene*-p-*sulphonylurea*.—This urea (2·9 g., 0·01 mol.), when heated at 210—200° for ½ hour, gave a clear melt, from which phenyl *iso*cyanate was evolved. The cooled material was boiled with successive portions of water (20, 5, and 5 ml.). The small insoluble residue (0·4 g.) was *s*-diphenylurea, m. p. 237—238° (Found : N, 13·1. Calc. for $C_{13}H_{12}ON_2$: N, 13·2%). From the aqueous extracts toluene-*p*-sulphonamide (1·2 g., 70%) was isolated.

Interaction of Phenylurea and Toluene-p-*sulphonyl chloride*.—(a) *Vigorous conditions*. An intimate mixture of powdered phenylurea (6·8 g., 0·05 mol.) and toluene-*p*-sulphonyl chloride (19·0 g., 0·1 mol.) was inserted into an oil-bath at 160° and kept at 155—165° for 15 minutes. Reaction set in vigorously as soon as the melt reached a temperature of 145—150° and hydrogen chloride was evolved. The effervescence slackened after 12—15 minutes; when reaction ceased the dark-brown reaction mixture was allowed to cool to 50°. The solidified cake was heated with chloroform (100 ml.), giving a purple solution, from which a white crystalline solid was filtered off. Crystallisation of this material (4·2—4·5 g.) from ethanol (50 ml.) gave lustrous white blades of ammonium toluene-*p*-sulphonate, m. p. 339—340° (decomp.) [Found : C, 44·3; H, 5·95; N, 7·4; S, 16·85%; *M*, 195 (volumetric). Calc. for $C_7H_{11}O_3NS$: C, 44·4; H, 5·8; N, 7·4; S, 16·9%; *M*, 189].

The chloroform filtrate A was exhaustively extracted with sodium hydroxide solution (3 × 60 ml.; 3% w/w) (extracted chloroform layer = B). The collected extracts, when filtered with carbon, and slowly acidified to Congo-red at 0°, gave a white crystalline precipitate of toluene-*p*-sulphonanilide, m. p. 101—103° (4·6 g.). The residual chloroform extracts B were washed until neutral and quickly evaporated in a vacuum. The residue was taken up in ethanol (25 ml.) and deposited white needles of *s*-diphenylurea, m. p. 235—236° (1·2 g.). The filtrate therefrom contained small quantities of unchanged toluene-*p*-sulphonyl chloride (m. p. 69—72°), identified by conversion into the amide (m. p. 136°).

(b) *Moderate conditions*. A mixture of phenylurea (6·8 g., 0·05 mol.) and toluene-*p*-sulphonyl chloride (14·3 g., 0·075 mol.) was carefully melted and stirred mechanically at 100° for 2 hours. The melt was dissolved in sodium hydroxide solution (10%; 60 ml.) at 70°, filtered from a small quantity of insoluble material (0·3 g.), cooled to 0°, and slowly addded to acetic acid (50% w/w; 40 ml.) at 0°. The white flocculent material which separated coagulated to a viscous oil, and solidified to a wax-like solid on storage. Since crystallisation proved difficult, the whole acid-insoluble fraction (4·2 g.) was methylated by dissolving it in sodium hydroxide (100 ml.; 10% w/w) and adding dimethyl sulphate (20 g.) in 4 portions at 70°. The separated product (3·2 g.) was methyltoluene-*p*-sulphonanilide, m. p. 94—95° (from ethanol). The alkaline filtrate therefrom was acidified and deposited a small quantity (0·3 g.) of white product of indefinite m. p. (150—180°).

Control experiments showed that *N*-phenyl-*N'*-toluene-*p*-sulphonylurea is neither methylated by methyl sulphate nor affected by 10% sodium hydroxide solution under the above conditions, and if formed should therefore be contained in the alkaline filtrate from the methylation.

Action of Dehydrating Agents.—(*a*) When solutions of *N*-phenyl-*N'*-toluene-*p*-sulphonylurea (1·45 g., 0·005 mol.) in pyridine (10 ml.) were treated with toluene-*p*-sulphonyl chloride (3·8 g., 0·02 mol.) and kept at room temperature, or at 60—80°, for 15 minutes, the sulphonylurea was recovered unchanged.

(*b*) The sulphonylurea was not affected when its solution in thionyl chloride was set aside at room temperature for 1 hour. Interaction with thionyl chloride or phosphorus oxychloride in pyridine at 100° gave intractable orange oils.

(*c*) A solution of *N*-phenyl-*N'*-toluene-*p*-sulphonylurea (1·45 g., 0·005 mol.) in excess of phosphorus oxychloride (10 ml.) was boiled under reflux until it separated into two phases (12—15 minutes; more prolonged refluxing caused partial decomposition). The cooled reaction mixture was slowly added to ice-water (100 ml.); on continued stirring, the excess of phosphorus oxychloride decomposed, leaving a white crystalline residue of toluene-*p*-sulphonyl chloride, (0·78 g., 82%), m. p. (after crystallisation) 69—70°, identified by conversion into the amide, m. p. 136—137°. The aqueous filtrate from the acid chloride contained aniline.

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Royal Free Hospital School of Medicine
(University of London), W.C.1.

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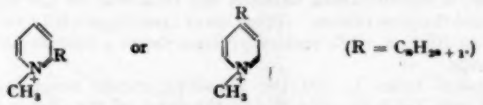
282. *Chemical Constitution and Surface-active Properties. 2-Alkylpyridines and 2-Alkyl-1-methylpyridinium Iodides.*

By M. J. Birchenough.

The hydrochlorides and methiodides of a number of 2-alkylpyridines have been examined for their effect on aqueous surface tension and for their antibacterial power. Maximum activity in both respects was exhibited by the salts of 2-pentadecylpyridine.

Extensive investigations have been carried out on the properties of quaternary ammonium germicides containing a long alkyl group attached directly to nitrogen, for example, cetyltrimethylammonium bromide (CTAB) and cetylpyridinium chloride (CPC). Few data are available, however, on compounds in which the alkyl group is connected to the nitrogen atom through a ring system, as in the alkylpyridinium salts yielding cations of the type :



The discovery by Tschitschibabin (*Bull. Soc. chim.*, 1936, **3**, 1607; 1938, **5**, 429) of a general method for the preparation of the higher homologues of pyridine made available a series of bases having valuable physical and biochemical properties. The method, involving the interaction of 2- or 4-methylpyridine with alkyl halides in the presence of sodamide was applied by Knight and Shaw (*J.*, 1938, 682) to the preparation of 2-alkylpyridines having side-chains of 13—19 carbon atoms. The authors indicated that the salts of these bases with strong acids resembled soaps in producing foaming solutions in water and acting as emulsifying agents. Subsequently Barkovsky (*Ann. Chim.*, 1944, **19**, 487) prepared further members of the series and reported on some of their properties, especially their high antibacterial activity (for the 2-*n*-alkyl series, results were given for $n = 12$ and 19). Values found for the effect on aqueous surface tension of one member of the series ($n = 19$) indicated that the hydrochlorides possess marked surface activity. Comparative values for the wetting power of a few of the alkylpyridinium salts are also given in U.S.P. 2,247,266.

In order to make a systematic comparison of their properties, eight 2-*n*-alkylpyridines have now been prepared with side-chains containing from 8 to 19 carbon atoms. Their salts have been examined for their effect on aqueous surface tension and their antibacterial power. Since Barkovsky had reported (*loc. cit.*) that 2-nonadecylpyridine could be readily converted into the methiodide, the bases were refluxed with methyl iodide at atmospheric pressure. Although the long alkyl group adjacent to the nitrogen atom might be expected to have a sterically hindering effect, all the bases reacted readily under these conditions. It is noteworthy that, whereas those containing a side-chain of more than 11 carbon atoms gave stable crystalline derivatives, the products obtained from the lower members were not stable : thus, 2-undecylpyridine gave a solid which darkened and decomposed on storage. Although moderately soluble in hot water, the methiodides are sparingly soluble at room temperature (of the order of 0·01% w/v at 20° for the higher members). It is also of interest that aqueous solutions of the higher alkylpyridine methiodides give only a slight immediate precipitate on treatment with silver nitrate : silver iodide is only slowly precipitated; the process is more rapid in the presence of nitric acid.

Adam and Shute (*Trans. Faraday Soc.*, 1938, **34**, 758) have pointed out that with dilute solutions of such compounds as cetylpyridinium chloride a very slow fall in surface tension takes place and the final values are often not reached for a week. Further, the final tension is to some extent independent of the concentration of the solution down to high dilutions.

It seems probable that the same effect should apply to the 2-alkylpyridinium salts, but this could not easily be allowed for when using the given technique : the above authors showed that the ageing effect applies to the surface only and not to the solution as a whole; if the solution is kept for a week and a fresh surface is formed, the same slow fall occurs. Thus the results reported here for the more dilute solutions are not to be regarded as absolute values. However,

since the *relative* effect is under examination, the objection is less serious, particularly since Adam and Shute also showed that there is a critical concentration for each compound at which the final value is reached almost immediately, and the value is dependent on chain length.

Of the five methiodides examined, that of 2-pentadecylpyridine showed the greatest effect; although at concentrations of M/5000 and M/10,000 the two higher homologues gave a greater depression, the minimum value obtained was 41 dynes/cm. for both these compounds, as compared with the 33 dynes/cm. given by the other methiodides.

The values obtained for the surface tensions of the bases in hydrochloric acid are in general lower at corresponding concentrations than for the methiodides. A notable feature of the behaviour of the higher members (from tridecylpyridine) is the persistence of the minimum value to very great dilutions; this is particularly evident in the case of pentadecylpyridine, which again gave the greatest effect. In this connection it is of interest that Adam and Shute (*loc. cit.*) also reported that in the presence of inorganic salts the final values were reached far more rapidly (see also Hill and Hunter, *Nature*, 1946, **158**, 585). This may account for the much greater persistence of the minimium value on dilution in the case of the acid solutions of the bases, as compared with the methiodides, the presence of the acid causing the final value to be reached more quickly.

An interesting point is the difference between the behaviour of the higher members and that of octyl-, nonyl-, and decyl-pyridines. These lower homologues fail to show the persistence of the minimum value on dilution, while undecylpyridine shows a transitional type of behaviour between these two groups.

Bacteriological Results.—Series I: Of the 2-*n*-alkylpyridine bases, hydrochlorides, and methiodides examined (see Table I), only the methiodides of the higher members (alkyl = tridecyl, pentadecyl, heptadecyl, and nonadecyl) showed outstanding bacteriostatic activity, and of these pentadecylpyridine methiodide gave considerably the greatest effect. In the presence of 10% serum the antibacterial activity was very markedly lowered.

The hydrochlorides of the higher members had no bacteriostatic effect against *Staph. aureus* or *Escherichia coli* at 1 : 5000, the highest concentration used. It is not surprising that these salts should be so much less active than the methiodides, since at the dilutions used the hydrochlorides must be very largely hydrolysed, leaving only a small proportion in the form of the active cation. Nevertheless, it is noteworthy that the free bases themselves (lower members) showed a moderate activity against *Staph. aureus*. In the presence of 10% of serum this fell to a figure of the order of 1 : 6000 which was common throughout the series of active compounds.

Series II: In a comparison of 2-pentadecylpyridinium methiodide, cetyltrimethylammonium bromide, and phenol, the variation between the values for each substance was very large (this is not uncommon: see Lawrence, "Quaternary Ammonium Germicides," 1950). Nevertheless the following general conclusions can be drawn: pentadecylpyridine methiodide is considerably more active than cetyltrimethylammonium bromide against *Staph. aureus* and also against *E. coli*, which is far more resistant. In general the activity of both compounds is much reduced in the presence of serum.

Series III, A and B: These series comprised tests of the bactericidal (as opposed to the bacteriostatic) properties. The values are to some extent dependent on experimental conditions (*e.g.*, composition of media and strain of test organism), and the comparison with literature values should be made with this reservation. In the comparison of the alkylpyridinium salts (series A), the differences appear rather smaller than in the bacteriostatic tests, but again the three higher methiodides show relatively high activity, of the same order as that of cetylpyridinium chloride. The comparison (series B) indicates a greater potency for pentadecylpyridine methiodide than for cetyltrimethylammonium bromide; the difference in activity between the two compounds is much smaller than under the conditions of the bacteriostatic tests (Table II) where the period of exposure was 24 hours.

Attempts have frequently been made to relate surface activity and antibacterial power (see, for example, Lawrence, *op. cit.*; Glassman, *Bact. Rev.*, 1948, **12**, No. 2). It is generally accepted that the action of antibacterial compounds is not to be explained solely in terms of their effect on surface tension: thus solutions of compounds of differing chemical types having comparable surface tensions differ widely in their antibacterial power. However, when comparing the members of a single series it is interesting that for the 2-alkylpyridinium salts the point of maximum activity coincides for surface activity and antibacterial power. 2-Pentadecylpyridine can be regarded as containing a chain of 16 carbon atoms attached to the quaternary nitrogen atom (since the side-chain is linked to nitrogen through one of the carbon atoms of the ring); in this respect it is analogous to cetylpyridinium chloride.

Experimental.

Preparation of 2-n-Alkylpyridines.—2-*n*-Octyl-, -nonyl-, decyl-, -undecyl-, -tridecyl-, -pentadecyl-, -heptadecyl-, and -nonadecyl-pyridine were prepared by Knight and Shaw's method (*loc. cit.*). 2-Nonyl- and 2-decylpyridine appear to be new :

2-*n*-Nonylpyridine, b. p. 128°/3·5 mm., gives a *picrate*, m. p. 55° (Found : C, 54·9; H, 6·3; N, 12·6. $C_{20}H_{26}O_7N_4$ requires C, 55·3; H, 6·0; N, 12·9%).

2-*n*-Decylpyridine, b. p. 138°/3 mm., gives a *picrate*, m. p. 67° (Found : C, 56·35; H, 6·2; N, 13·0. $C_{21}H_{28}O_7N_4$ requires C, 56·3; H, 6·25; N, 12·5%).

Methiodides.—The base was refluxed with excess of methyl iodide for 2 hours and the excess of iodide distilled off *in vacuo*. The residue was twice extracted with boiling ether, and recrystallised from ethyl acetate. The following appear to be new :

2-n-*Tridecyl-* (Found : I, 31·4. $C_{19}H_{34}NI$ requires I, 31·5%), 2-n-*pentadecyl-* (Found : I, 28·9. $C_{21}H_{38}NI$ requires I, 29·5%), and 2-n-*heptadecyl-pyridine methiodide* (Found : I, 28·2. $C_{23}H_{42}NI$ requires I, 27·7%). These and 2-*n*-nonadecylpyridine methiodide (Found : I, 26·9. Calc. for $C_{25}H_{46}NI$: I, 26·1%) softened at *ca.* 87°, except that 2-tridecylpyridine methiodide softened at 77°.

Fig. 1.

2-Alkylpyridines in 0·5N-HCl at 25°.

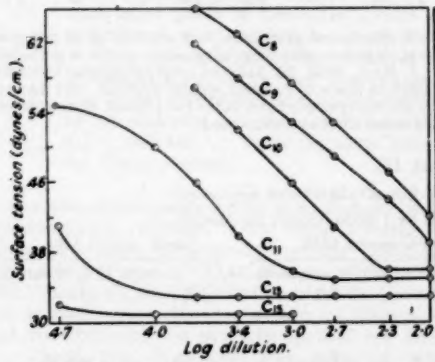
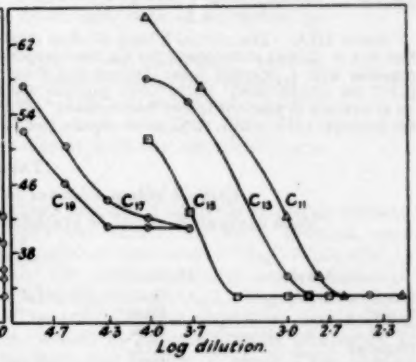


Fig. 2.

2-Alkylpyridine methiodides in water at 25°.



Surface Tension.—Determinations were carried out at 25° with the du Noüy tensimeter, readings being taken after 15 minutes' equilibration. In addition to measurements on aqueous solutions of the methiodides (Fig. 2), readings were taken for solutions of the bases (or their hydrochlorides) in 0·5N-hydrochloric acid (Fig. 1). In this way the comparison could be extended to the bases which did not give stable methiodides. To avoid complications caused by variation in the degree of hydrolysis on

Table I.

Highest dilution giving bacteriostatic effects of 2-alkylpyridine derivatives.

Each figure given should be multiplied by 1/1000.

50% Inhibition after 18 hrs. at 37° in 2% glucose broth.

		Staph. aureus 4163		*Staph. aureus* 2301		*E. coli* 86		Complete inhibition.	
Alkyl.	Derivative.		with 10% of serum.		with 10% of serum.		with 10% of serum.	*Staph. aureus* 4163.	*E. coli* 86.
Octyl	Base	1/12	1/6	1/12	1/6	—	—	1/8	—
Nonyl	Base	1/100	,,	>1/32	,,	—	—	1/64	—
Decyl	Base	1/24	,,	,,	,,	—	—	1/16	—
Undecyl ...	HCl	1/150	,,	,,	,,	—	—	1/100	—
Tridecyl ...	HCl	>1/5	>1/5	—	—	>1/5	>1/5	—	>1/5
,, ...	MeI	1/1200	1/7	—	—	1/30	,,	1/800	1/5
Pentadecyl	HCl	>1/5	>1/5	—	—	>1/5	,,	—	>1/5
,,	MeI	1/6000	1/7	—	—	1/60	,,	1/3200	1/5
Heptadecyl	HCl	>1/5	>1/5	—	—	>1/5	,,	—	>1/5
,,	MeI	1/2400	1/15	—	—	1/15	,,	1/1600	1/10
Nonadecyl	HCl	>1/5	>1/5	—	—	>1/5	,,	—	>1/5
,,	MeI	1/1200	1/15	—	—	1/15	,,	1/800	1/10

dilution, the original solutions were diluted with acid of the same concentration. No curves were drawn for heptadecyl- or nonadecyl-pyridine in acid solution, since the compounds gave values of 37—38 and 35—36 dynes/cm. respectively at all concentrations down to M/100,000.

Bacteriological.—Series I. The bacteriostatic effects of the compounds on *Staph. aureus* and *E. coli* are listed in Table I.

Because of their low solubility in water at room temperature, the compounds were dissolved in a few drops of alcohol and diluted with water to give colloidal solutions or fine suspensions. These were used for serial dilutions in 2% glucose broth at pH 6·8; for such dilutions one loopful of test organism was used as inoculum, and incubation was at 37°.

Series II. Since 2-pentadecylpyridine methiodide (PPM) showed considerably the greatest activity, it was compared with phenol and cetyltrimethylammonium bromide (CTAB). Table II shows concentrations necessary for complete inhibition of growth for 24 hours at 37° in glucose broth at pH 6·8.

TABLE II.

2-*n*-Pentadecylpyridine methiodide	*Staph. aureus* 4163.						*E. coli*.					
				with 10% of serum.						with 10% of serum.		
	I.	II.	III.	I.	II.	III.	I.	II.	III.	I.	II.	III.
(PPM) ...	1/3200	1/51,000	1/25,600	1/7	>1/16	1/64	1/60	1/32	1/64	>1/5	—	1/2
CTAB	—	1/800	1/3200	—	>1/16	1/80	—	>1/2	>1/2	—	<1/2	>1/2
Phenol	—	5	3	—	5	5	—	2·5	2·5	—	5	2·5

Series IIIA. The critical killing dilution (highest dilution of germicide that will kill in 10 minutes but not in 5) was determined for all the compounds, together with that of phenol, which is included together with a recorded value (Quisno and Foter, *J. Bact.*, 1946, **52**, 111) for cetylpyridinium chloride (CPC) for comparison. Bacto-Difco peptone was used in place of Armour special peptone, and Lemco meat extract in place of Liebig beef extract. With the exception of the value for phenol, figures given are accurate only within 30%, since usually two-fold serial dilutions were used.

TABLE III.

Critical killing dilutions for 2-n-*alkylpyridine derivatives.*

[Each figure given should be multiplied by 1/1000 (except for phenol).]

Alkyl.	Derivative.	*Staph. aureus* 4163.		*Staph. aureus* 2301	
			with 10% of serum.		with 10% of serum.
Octyl	Base	>1/1	>1/1	>1/1	>1/1
Nonyl	Base	,,	,,	,,	,,
Decyl	Base	,,	,,	,,	,,
Undecyl	HCl	,,	,,	,,	,,
Tridecyl	HCl	>1/10	>1/10	>1/10	>1/10
,, ...	MeI	,,	,,	,,	,,
Pentadecyl	HCl	>1/10	>1/10	>1/10	>1/10
,, ...	MeI	1/80	,,	1/80	1/20
Heptadecyl	HCl	>1/10	,,	>1/10	>1/10
,, ...	MeI	1/80	,,	1/240	1/40
Nonadecyl	HCl	>1/10	,,	1/40	>1/10
,, ...	MeI	1/80	,,	1/120	1/30
CPC *		1/83	1/12·5	—	—
Phenol		1/96	1/72	—	—

* Average of 5 *Staph.* strains.

Series IIIB. The following table shows finally a further comparison of the critical killing dilutions of PPM, CTAB, and phenol, made by Hoogerheide's method (*J. Bact.*, 1945, **49**, 277), against *Staph. aureus*. The suspension of *Staph. aureus* was diluted 10 times in phosphate buffer at pH 8 containing the germicide.

Critical killing dilutions—using Staph. aureus.

(Figures to be multiplied by 1/1000.)

	I.	II.	III.
PPM	1/80	1/50	1/64—1/80
CTAB	—	>1/16	1/25
Phenol	—	12·5	12·5

The author is indebted to Miss J. L. Ward of Roche Products, Ltd., for the bacteriological work, and to Professor H. Burton for much valuable advice and criticism.

KING'S COLLEGE OF HOUSEHOLD AND SOCIAL SCIENCE
(UNIVERSITY OF LONDON), CAMPDEN HILL ROAD, W.8. [*Received, January 6th*, 1951.]

283. *The Hydrothermal Chemistry of Silicates. Part I. Synthetic Lithium Aluminosilicates.*

By R. M. Barrer and E. A. D. White.

The formation of crystalline lithium aluminosilicates, and to a lesser extent of silicates and aluminates, has been studied by hydrothermal methods over the temperature range 150—450°.

Known species synthesised in this range include boehmite, α-petalite, α- and β-eucryptite, α- and β-spodumene, γ-alumina, and α-quartz. A lithium aluminate similar to but not identical with the spinel $LiAl_5O_8$ was found; and also a lithium silicate, Li_2O,SiO_2, previously grown elsewhere by pyrolytic methods. In the lithium aluminosilicate field, in addition to the minerals mentioned above, species of composition $Li_2O,Al_2O_3,2SiO_2,4H_2O$ (A), and $Li_2O,Al_2O_3,8SiO_2,5H_2O$ (H) were produced in major yields, together with lesser yields of two other species. These have been characterised by optical and, where possible, by *X*-ray studies.

Thermal stability of the minerals A and H was examined; ignition produced β-eucryptite and β-spodumene, respectively. The minerals A and H also showed the sorptive behaviour of zeolites, and underwent a variety of ion-exchange reactions involving Li^+, Ag^+, Na^+, K^+, Rb^+, Tl^+, NH_4^+, Ca^{++}, and Ba^{++}. These reactions were followed optically, chemically, and by *X*-ray methods.

A feature of the geochemistry of lithium is the limited number of naturally occurring lithium aluminosilicate minerals. Only three minerals composed entirely of lithia, alumina, and silica have been discovered: petalite ($Li_2O,Al_2O_3,8SiO_2$), spodumene ($Li_2O,Al_2O_3,4SiO_2$), and eucryptite ($Li_2O,Al_2O_3,2SiO_2$). These, with the lithia-containing micas lepidolite $[(HO,F)_2,(Li,K)_3,Al_2Si_3O_9]$ and zinnwaldite $[(HO,F)_2,(Li,K)_3,FeAl_2Si_3O_{14}]$, comprise almost all the naturally occurring species rich in lithium. The crystallisation of petalite, spodumene, and eucryptite by the pyrolytic method has been claimed by various workers (Hautefeuille and Perrey, *Bull. Soc. franç. Min.*, 1890, **13**, 145; Ballo and Dittler, *Z. anorg. Chem.*, 1912, **76**, 39; Winkler, *Acta Cryst.*, 1948, **1**, 27). Following an unsuccessful attempt at hydrothermal crystallisation by Hatch (*Amer. Min.*, 1943, **28**, 471), all three minerals have been recently synthesised in their low-temperature forms (Roy, Roy, and Osborne, *J. Amer. Ceram. Soc.*, 1950, **33**, 152). Pyrolytic crystallisations of melts containing lithia, alumina, and silica have been reported to give several synthetic species (Weyberg, *Centr. Min.*, 1905, 646; Hautefeuille and Perrey, *loc. cit.*; Ballo and Dittler, *loc. cit.*), and Thugutt (*Z. anorg. Chem.*, 1892, **2**, 64, 113) reported a hydrothermal preparation of crystals of composition $Li_2O,Al_2O_3,2SiO_2,2H_2O$. Too little information is given concerning these synthetic species, however, for their subsequent recognition. Work, often of a rather conflicting nature, has also been carried out in the lithium silicate and lithium aluminate fields (Hautefeuille and Margottet, *Bull. Soc. franç. Min.*, 1881, **4**, 175; Ballo and Dittler, *loc. cit.*; Noll, *Neues Jahrb. Min. Geol.*, Beil. Bd., 1935, **70**, 65; Kracek, *J. Amer. Chem. Soc.*, 1939, **61**, 2870; Hatch, *loc. cit.*; Austin, *J. Amer. Ceram. Soc.*, 1947, **30**, 219; Rustrum Roy and Osborne, *J. Amer. Chem. Soc.*, 1949, **71**, 2086).

The present investigation was undertaken, as part of a programme concerned with the synthetic hydrothermal chemistry of the aluminosilicates, to improve understanding of growth conditions and of diversity among such lithium compounds. A particular object was to find whether lithium zeolites can be crystallised from gels. Natural zeolites contain only sodium, potassium, calcium, and barium as interstitial cations, although a number, but not all of them (*e.g.*, chabazite and mordenite), can exchange considerable amounts of these cations for lithium under hydrothermal conditions. One may question whether the unusually open character of the aluminosilicate framework of zeolites is fully compatible during growth with the small size of the lithium ion, and attempt to answer this question by successful crystallisation of lithium zeolites.

The investigation also represents an attempt to determine whether the lack of diversity of natural lithium aluminosilicates can be attributed to the lesser amount of this element than of sodium or potassium in the lithosphere, resulting in a failure of natural processes to

segregate lithium under mineralising conditions. If this is the only reason for such lack of diversity, then under laboratory conditions a good variety of aluminosilicates could be expected.

Knowledge of synthetic lithium aluminosilicates has been obtained mainly by the pyrolytic method. Until recently their hydrothermal chemistry has been little studied. Moreover, zeolites grow under alkaline hydrothermal conditions, which also favour the formation of well-developed crystals. For these reasons the hydrothermal method was used here as the normal method of synthesis and crystal growth.

Experimental.

Lithium hydroxide was prepared by the reaction $Li_2SO_4 + Ba(OH)_2 = 2LiOH + BaSO_4\downarrow$. The hydroxide was made and stored in absence of carbon dioxide. Aluminium hydroxide was obtained by the action of water on lightly amalgamated aluminium (Wislicenus, *Z. anorg. Chem.*, 1904, **17**, 805; Weiser and Milligan, *Chem. Revs.*, 1939, **25**, 1). The product was washed with alcohol and ether, and air-dried. Ignition loss corresponded to $Al_2O_3.3H_2O$. Silica gel was supplied by B.D.H. Ltd., as silicic acid containing ~15% of SiO_2. Hydrothermal extraction of a sample at 250° gave a mother-liquor neutral and free from common inorganic cations. *X*-Ray powder photographs of the aluminium hydroxide and silicic acid showed that both were amorphous.

The series of gels $Li_2O,Al_2O_3,nSiO_2,mH_2O$, in which n varied between 1 and 10, were made by mixing the constituents in the correct proportions and evaporating the mixtures to dryness at 120°. The dried products were ground and stored under carbon dioxide-free conditions. Hydrothermal crystallisations were carried out by mixing 2 g. of gel with 10 c.c. of water or ~N-lithia solution in stainless-steel autoclaves of ~20 c.c. internal capacity (Barrer, *J.*, 1948, 127). Autoclaves were then heated in air ovens with thermostatic control, operating up to 300°. For higher temperatures a specially designed thermostatted furnace was employed, capable of holding up to nine autoclaves. Most experiments were left for 36—60 hours for crystallisation to occur, although at the lowest temperatures (<150°) 3—4 days were given. In a few experiments carried out above 450° good yields of large crystals appeared in less than 2 hours.

After the crystallisation period, the autoclaves were quenched in cold water, the pH value of the cold mother-liquor was measured to the nearest 0·2 pH unit, and the insoluble reaction products were collected for further examination.

Examination of Products.—Optical examination was carried out by means of Vickers projection and Leitz polarising microscopes. Refractive indices (in sodium light) were measured in most cases to within ±0·002 unit; extinction angles were also observed; and in the case of favourably large crystals, interference figures were studied.

X-Ray powder photographs were taken of the products which were formed in high enough yields, a Hilger HRX unit operating with 9-cm. cameras being used. Nickel-filtered Cu-K_α radiation was used throughout. Where possible the probable unit-cell dimensions were determined by means of logarithmic Bjurstrom charts. This method carried out for synthetic quartz gave dimensions within 1% of the accepted values.

Investigation of the sorptive properties of the crystals was carried out in a simplified modification of Barrer and Ibbitson's apparatus (*Trans. Faraday Soc.*, 1944, **40**, 195, 206). Only crystals with water of constitution were so examined, the sample being first outgassed between 200° and 300° for 24 hours. Gases used in these experiments were: ammonia, propane, hydrogen, nitrogen, and helium. The last three were obtained from the British Oxygen Co., in the pure state; propane was taken from a cylinder, dried, and fractionated; and ammonia was prepared by warming quick-lime and ammonium chloride in an evacuated flask, drying the evolved gas by passing it through a column of quick-lime, and fractionating it.

Ion-exchange reactions were studied using chlorides, nitrates, or nitrites of Li, Na, K, Rb, Cs, Ca, Ba, Ag, Tl, and NH_4. Hydrothermal, fusion, and vapour-phase exchange procedures were employed (Barrer, *J.*, 1950, 2342). Hydrothermal exchanges involved heating the crystals with aqueous solutions of the desired salts (the salt being in excess) in sealed glass tubes at 120° for about 2 days. During exchange, the tubes were rotated continuously in a thermostatted air oven. Above 120° recrystallisation was frequently observed, but much below it the rates of exchange were often low. Exchange reactions by fusion were limited to silver nitrate and barium nitrite, since the lithium aluminosilicates showing exchange properties underwent irreversible thermal lattice changes at 300°. The fusion method was found very effective. Vapour-phase exchange was restricted to NH_4^+ (Clark and Steiger, *Amer. J. Sci.*, 1902, **13**, 27; *Z. anorg. Chem.*, 1902, **29**, 338). A preliminary outgassing of the specimens was needed to prevent evolved water from bursting the glass reaction tubes. The method, however, proved less successful with the lithium aluminosilicates than with most zeolitic species.

Ion-exchange products were washed free from exchanging salt, dried, and examined by *X*-ray, optical, and chemical methods.

Analytical results were in many cases difficult to interpret because of varying amounts of uncrystallised gel or of alternative species. Attempts were made to separate the required crystals by various methods, but only partial success was obtained. Accordingly, analytical data were collected primarily for species which appeared in nearly 100% yield. Standard methods were used for determination of silica, alumina, and metallic ions, decomposition of the minerals being effected by sodium carbonate fusion, or by treatment on a steam bath with 1 : 1 nitric or hydrochloric acid. Lithium was determined

after removal of silica and alumina. The residual salts were converted into chlorides, and the lithium chloride extracted with *iso*amyl alcohol in a modified Soxhlet apparatus.

Results.

The Alumina Field.—In order to simplify the investigation in the field of compositions Li_2O–Al_2O_3–SiO_2–H_2O, preliminary study was made in the fields Li_2O–Al_2O_3–H_2O and Li_2O–SiO_2–H_2O. In this way it was hoped that products in these fields could be identified and thus recognised if again encountered among the lithium aluminosilicates. The results of experiments in the alumina field are given in Table I. It is seen that treatment of aluminium hydroxide with water or lithium hydroxide yielded boehmite, a lithium aluminate, and γ-alumina. Boehmite was found over the whole range 130—450°, its formation being favoured by lower pH values, although some boehmite appeared also in specimens treated with lithia water, especially at lower temperatures. Lithium aluminate appeared between 160° and 450°, with optimum yields at 300°. At 450° in media of high pH values γ-alumina crystallised in varying quantities.

TABLE I.

Reactants.	Temp.	Products.
$Al(OH)_3$ + LiOH, aq.	130°	Mostly *boehmite*, small crystals.
$Al(OH)_3$ + LiOH, aq.	160	*Boehmite*, with some *lithium aluminate*.
$Al(OH)_3$ + aq.	250	*Boehmite*, moderate yield, very small crystals.
$Al(OH)_3$ + LiOH, aq.	250	*Boehmite*, with some *lithium aluminate*.
$Al(OH)_3$ + LiOH, aq.	310	*Lithium aluminate*, good yield.
$Al(OH)_3$ + aq.	360	*Boehmite*, very good yield of large crystals.
$Al(OH)_3$ + LiOH, aq.	360	*Lithium aluminate*, moderate yield.
$Al(OH)_3$ + aq.	420	*Boehmite*, good yield.
$Al(OH)_3$ + Li_2SO_4, aq.	450	*γ-Alumina, boehmite*, some *lithium aluminate*.
$Al(OH)_3$ + LiOH, aq.	450	*γ-Alumina boehmite*, some *lithium aluminate*.
$Al(OH)_3$ + aq.	450	*Boehmite*, moderate yield of small crystals.

Some properties of the species crystallised in the alumina field are summarised below:

Synthetic boehmite (Plate I). The *X*-ray spacings of boehmite are recorded in Table IV, Noll's data (*loc. cit.*) being given for a second synthetic specimen. The crystals grew as irregular hexagonal plates up to 150 μ. in length. Birefringence moderate, straight extinction, negative elongation, biaxial positive, $\alpha = 1{\cdot}650$, $\beta = 1{\cdot}659$, $\gamma = 1{\cdot}670$. System orthorhombic. Optimum growth: $Al_2O_3 + H_2O$ at 400°. Analysis: $Al_2O_3.H_2O$. Recrystallised on ignition to α-Al_2O_3 (corundum). The refractive indices noted above are slightly higher than values in the literature (*e.g.*, Dana's "System of Mineralogy," 7th edn., Wylie & Sons).

γ-Alumina. The *X*-ray spacings of the γ-Al_2O_3 of Table I are compared in Table IV with those for γ-Al_2O_3 given in the "Alphabetical Index of *X*-Ray Diffraction Data." The crystals grew as cubes of indefinite outline up to 15 μ. long, isotropic, n ~1·70. Conditions of growth: $Al(OH)_3 + H_2O$ at 450°; usually mixed with boehmite.

Lithium aluminate (Plate II). *X*-Ray spacings in Table IV give over 20 lines in agreement with the spinel $Li_2O,5Al_2O_3$ (Kordes, *Z. Krist.*, 1935, **91**, *A*, 193), but there are some differences. The crystals grew as rectangular prisms up to 50 μ. long. Birefringence moderate; straight extinction; positive elongation, uniaxial, $\omega = 1{\cdot}620$, $\varepsilon = 1{\cdot}640$. System tetragonal. Optimum conditions of growth: $Al(OH)_3$ + excess LiOH, aq. at 300°. Usually mixed with boehmite. Hatch (*loc. cit.*) reported a product Li_2O,Al_2O_3, which is uniaxial negative, with $\omega = 1{\cdot}606$, $\varepsilon = 1{\cdot}624$.

TABLE II.

Reactants.	Temp.	Products.
$SiO(OH)_2$ + LiOH, aq.	160°	Masses of very small crystals of *lithium silicate*.
$SiO(OH)_2$ + aq.	250 (1 day)	Little or no crystallisation.
$SiO(OH)_2$ + aq.	250 (4 days)	Little or no crystallisation.
$SiO(OH)_2$ + LiOH, aq.	310	*Lithium silicate* in good yield.
$SiO(OH)_2$ + LiOH, aq.	360	*Lithium silicate*, moderate yield.
$SiO(OH)_2$ + aq.	450	*Quartz*, little *cristobalite*.
$SiO(OH)_2$ + Li_2SO_4, aq.	450	*Quartz*, good yield.
$SiO(OH)_2$ + LiOH, aq.	450	*Quartz*, good yield.

The Silica Field.—Silica gel, treated with excess of lithium hydroxide solution, crystallised to a lithium silicate (Li_2O,SiO_2) at 160° and 310°. The yield, however, decreased with rise of temperature until at 450° quartz became the primary phase. Treatment with water alone yielded no crystalline products at 250°, and at 450° small quartz crystals were formed together with small amounts of cristobalite. Table II records experiments in the silica field. The results in Tables I and II indicate that in the aluminosilicate field there will be little complication due to co-precipitation with alumino-

silicates of either aluminates or silicates of lithium. The lithium silicate of Table II was crystallised also from aluminosilicate gels (Table III), but was readily identified. The properties are given below.

TABLE III.

*Summary of results in aluminosilicate field.**

(Compositions $Li_2O,Al_2O_3,nSiO_2$.)

Temp.	$n = 1$.	$n = 2$.	$n = 3$.	$n = 4$.	$n = 5$.
130°	Good A 10·5	Good A 10·5	Poor A 10·5	Poor A 10·5	—
150—160	Good A 10·5	Good A 10·0	Mod. A 10·0	Poor A 10·5	Poor H 10·5
190	Good A 10·5 (Poor A>11)	V. good A 10·5 (Mod. A>11)	Good A 10·5 (Some A & D>11)	Poor A 10·5 (Some A & D>11)	Poor A 10·5 (Mod. D>11)
220—230	Good A 10·3 (Good A>11)	Good A 9·8 (Good A>11)	Mod. A 10·0 (Poor A; some D>11)	Poor A 9·8 (Some A & D~11)	Poor A & D 8·7 (Poor H~11)
250	Good A~10 (Mod. A>11)	Good A~10 (Mod. A>11)	Mod. A 9·7 (Mod. A>12)	Poor A 10·0) (Mod. A>11)	Poor A Some H~10 (Mod. A~10)
275	Mod. A 9·0 (Mod. A & B >11)	Mod. A 7·4 (Some B~11)	Mod. A 7·4 (Some B & E ~11)	Poor A 7·7 (Some B 10·5)	Poor A 7·7 (−10·5)
300	Some A & B 10·5 (Mod. B~11)	Mod. A Some B 8·7 (Mod. B~11)	Mod. A Poor B 8·7 (Some A & B 10·5)	Poor A Some B 8·0 (Poor A & B 10·5)	Poor A Some B 8·0 (Poor A 10·5)
330—340	Mod. B 8·5 (Mod. B~11)	Mod. B 7·4 (Good B~11)	Mod. B 6·1 (Mod. B~11)	Poor B Some A 7·4 (Mod. B~11)	Poor B 9·3 (Poor B~11)
360	Mod. B 8·8 (V. good B~11)	Good B 9·0 (V. good B 10·5)	Good B 10·0 (Good B~11)	Good B 7·7 (Good B 10·0)	Mod. B 8·0 (Mod. B 10·0)
390	Mod. B 10·5 (V. good B~11)	Good B 8·3 (V. good B 10·5)	Mod. B 8·0 (Good B 10·5)	Mod. B 9·0 (Mod B 10·5)	Poor B & C 10·0 (Poor C 10·0)
450	Good B 10·0	Good B 10·0	Mod. B & I 8·7	Some B & I 8·7	Some B & I 10·0
	$n = 6$.	$n = 7$.	$n = 8$.	$n = 9$.	$n = 10$.
130	—	—	—	—	—
150—160	V. poor H 10·5	Poor H 10·5	Poor H 10·5	V. poor H 10·5	10·5
190	Poor H 10·5 (Mod. D>11)	Poor H 10·5 (Poor D>11)	Poor H 10·5 (Poor H & D>11)	Poor H 10·5 (Poor H & D>11)	−10·5 −>11
220—230	Some A & D 10·0 (Some H~11)	Poor A & D 10·0 (Poor H~11)	Poor H 10·0 (Mod. H~11)	Poor H 10·0 (Mod. H~11)	V. poor H 10·0 (Mod. H~11)
250	Some A & H~10 (Mod. A 10·5)	V. poor H~10 (Some A 10·5)	Poor H~10 (Some D 10·5)	Poor H~10 (Poor D 10·5)	V. poor H~10 (Poor D 10·5)
275	Some A 7·4 (−10·5)	V. poor H 7·4 (Poor D 10·5)	Poor H 7·4 (Poor D 10·5)	Poor H 7·4 (Some D~10·5)	Poor H 7·4 (Some D~10·5)
300	Poor A 7·7 (Some A 10·5)	Some A Poor H 8·0 (Some A 10·5)	Mod. H 7·7 (−10·5)	Mod. H 7·7 (−10·5)	Poor H 8·0 (−10·5)
330—340	V. poor B 7·7 (Some B & C~11)	Poor C 8·3 (Some B & C~11)	Poor C 6·4 (Poor C~11)	Poor C 10·0 (Mod. C~11)	Poor C 7·4 (Poor C~11)
360	Poor B Mod. C 7·1 (Poor B & C 10·0)	Good C Some G 3·5 (Poor B. Mod. C 10·0)	Mod. C 3·6 (Good C 10·0)	Poor C 6·7 (Mod. C 10·0)	Poor C 4·2 (Mod. C 10·5)
390	Mod. C 10·0 (Mod. C 10·0)	Mod. C 10·0 (Good C 10·0)	Good C 10·0 (Good C 10·0)	Mod. C 10·0 (Mod. C 10·5)	Mod. C 10·0 (Mod. C 10·5)
450	V. poor B & I 9·6	Good C Poor I, 8·7	V. good C Some I 8·7	V. good C 8·7	—

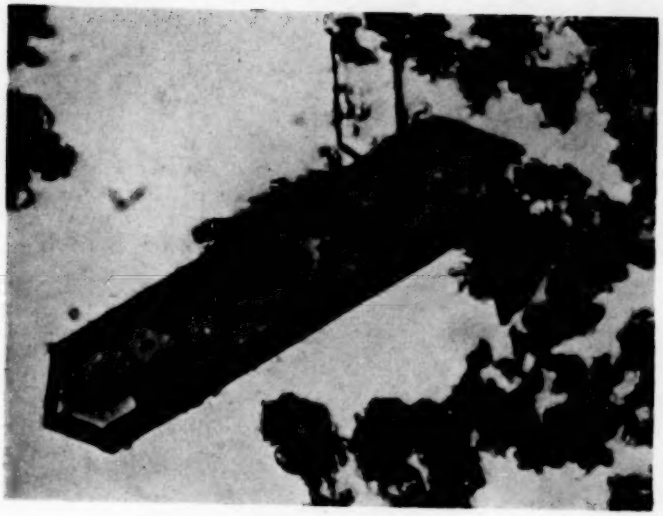
* Results recorded parenthetically are those of treatment of gels in presence of excess of LiOH solution.

Lithium silicate (Species D of Table III). *X*-Ray spacings in Table IV agree with those of the compound Li_2O,SiO_2 obtained by Austin (*loc. cit.*). Formed as radial clusters of long needle-like crystals up to 20 μ. in diameter, and also occurred as spherulites. Birefringent; straight extinction; positive elongation; probable system: tetragonal, $\varepsilon = 1{\cdot}599$, $\omega = 1{\cdot}587$. Unit cell dimensions $a = 9{\cdot}3_9$; $c = 5{\cdot}9_2$ A. Optimum growth: SiO_2 + excess LiOH, aq. at ~300°.

α-Quartz. Quartz was grown as hexagonal prisms up to 30 μ. long, showing moderate birefringence, straight extinction and being uniaxial negative; $\varepsilon = 1{\cdot}553$, $\omega = 1{\cdot}544$. Best condition of growth: SiO_2 + excess LiOH, aq. at 450°. Identified by *X*-ray spacings as α-quartz.

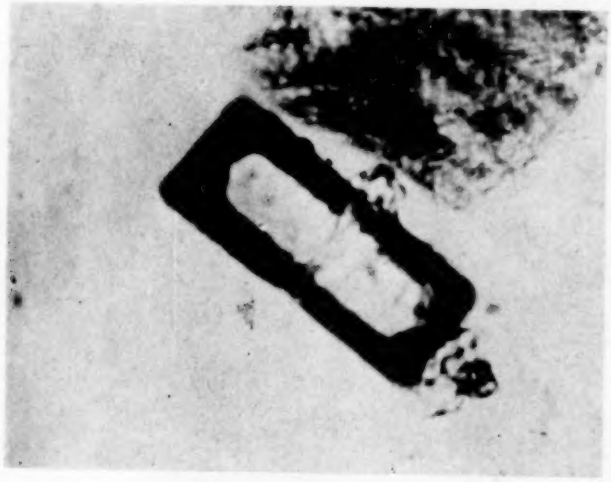
The Aluminosilicate Field.—Most of the work done with compositions $Li_2O,Al_2O_3,nSiO_2$ + aq. is summarised in Table III, in which the crystalline species are designated by letters A—J. The crystals

PLATE I.



Synthetic boehmite, × 1030.

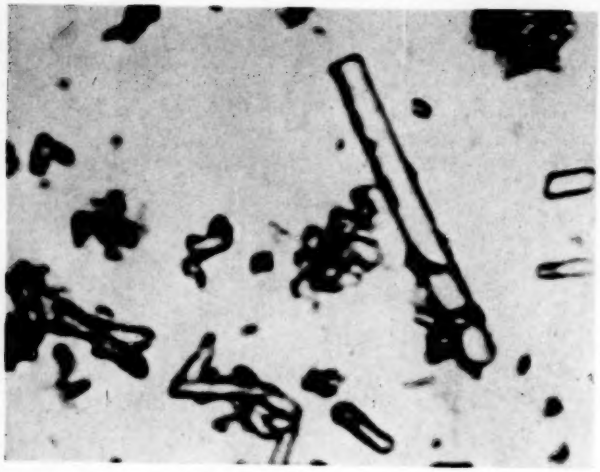
PLATE II.



Lithium aluminate, × 1520.

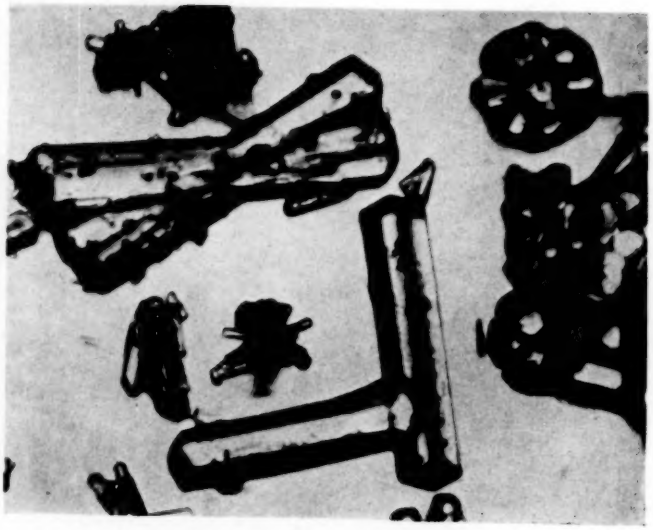
[*To face p.* 1270.

PLATE III.



Species A, × 1500.

PLATE IV.



Species B (*α-eucryptite*), × 820.

PLATE V.

Species C (*petalite*). × 640.

PLATE VI.

Species E, × 730.

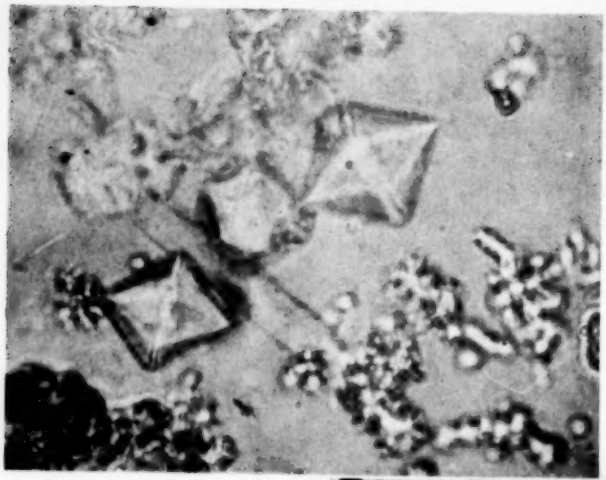
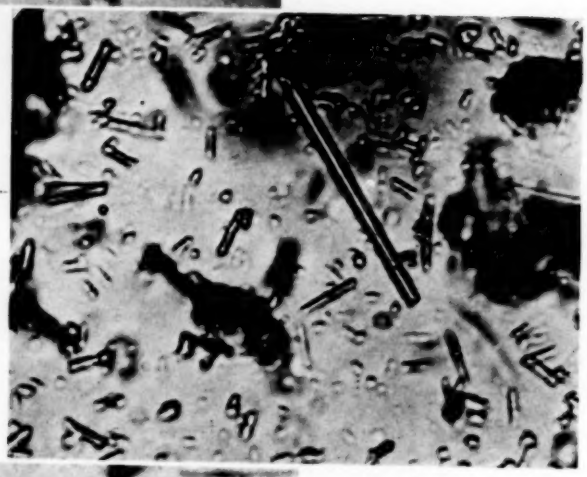


PLATE VII.

Species F (β-eucryptite), × 800.

PLATE VIII.

Species H, × 1500.



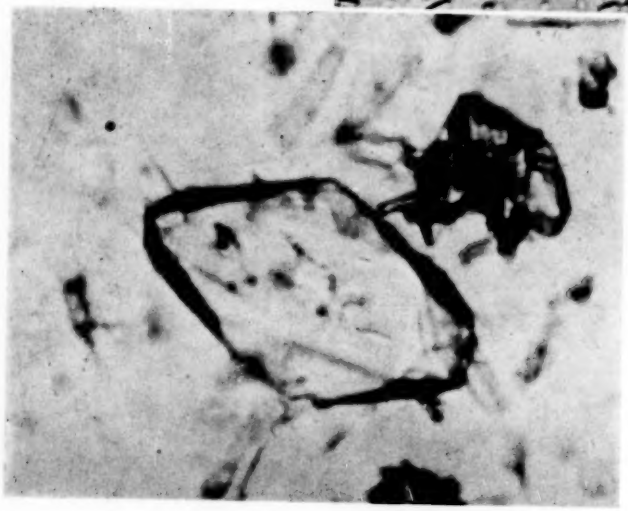


PLATE IX.

Species I (β-spodumene), × 1540.

TABLE IV.

X-Ray data (*spacings in* A.).

Species A.*		Species B * (α-eucryptite).		Species C (α-petalite).		Natural petalite.		Species D (lithium silicate).		Li_2O,SiO_2.†	
I.	*d.*	*I.*	*d.*	*I.*	*d.*	*I.*	*d.*	*I.*	*d.*	*I.*	*d.*
vs	6·42	s	6·92	w	5·48	w	5·45	—	—	0·02	5·32
mw	5·21	mw	4·32	mw	4·67	w	4·69	s	4·85	1	4·70
vs	4·29	vs	3·97	w	4·30	w	4·26	—	—	0·1	4·02
vw	4·06	w	3·59	m	4·02	—	—	s	3·39	0·72	3·32
vw	3·27	s	3·48	vvs	3·73	vvs	3·72	—	—	0·02	3·20
vs	3·15	s	3·37	ms	3·52	ms	3·54	s	2·74	0·74	2·72
vs	3·03	w	3·21	w	3·40	vw	3·36	—	—	0·13	2·66
s	2·490	w	3·14	vw	3·24	vvw	3·20	m	2·50	0·04	2·59
w	2·392	w	3·04	—	—	mw	3·11	s	2·35	0·19	2·35
m	2·326	s	2·74	m	3·00	m	2·99	w	2·11	0·05	2·10
vw	2·243	vs	2·55	mw	2·780	w	2·781	m	1·780	0·10	1·78
mw	2·173	vw	2·32	ms	2·578	m	2·576	m	1·663	0·12	1·66
w	2·042	m	2·25	vvw	2·503	vw	2·531	vw	1·625	—	—
mw	1·952	w	2·08	mw	2·408	mw	2·407	m	1·569	0·30	1·57
vw	1·868	vw	1·98	w	2·262	—	—	—	—	0·04	1·53
m	1·754	mw	1·946	ms	2·070	s	2·066	w	1·483	—	—
mw	1·725	ms	1·877	vvw	1·995	vvw	1·993	w	1·418	0·02	1·40
w	1·556	ms	1·803	s	1·939	ms	1·935	m	1·354	0·06	1·36
mw	1·524	m	1·635	m	1·899	m	1·895	m	1·300	0·12	1·30
m	1·474	mw	1·547	m	1·875	—	—	w	1·256	0·08	1·26
vw	1·445	w	1·526	vw	1·837	vvw	1·835	w	1·174	0·05	1·18
mw	1·405	m	1·490	w	1·807	w	1·803	w	1·137	0·05	1·14
vw	1·371	vw	1·441	vw	1·756	w	1·755	w	1·069	—	—
vw	1·348	vw	1·399	mw	1·726	w	1·722	w	1·022	—	—
vw	1·327	s	1·374	vw	1·632	m	1·629	w	1·001	—	—
vw	1·300	vw	1·348	w	1·640	—	—	—	—	—	—
w	1·270	m	1·321	—	—	vw	1·612	—	—	—	—
vw	1·244	m	1·295	vw	1·529	mw	1·522	—	—	—	—

Synthetic Li aluminate.		$LiAl_5O_8$.‡		Synthetic γ-Al_2O_3.		γ-Al_2O_3.*	
I.	*d.*	*I.*	*d.*	*I.*	*d.*	*I.*	*d.*
m	7·56	—	—	m	7·71	—	—
m	4·60	0·3	4·59	ms	4·64	—	—
m	4·05	—	—	m	4·09	—	—
m	3·85	—	—	m	3·87	—	—
vw	3·54	0·15	3·56	vw	3·15	—	—
m	2·80	0·5	2·81	s	2·82	0·6	2·80
m	2·70	0·1	2·67	m	2·72	—	—
vw	2·625	—	—	mw	2·63	—	—
vw	2·462	—	—	vw	2·54	—	—
s	2·383	1·0	2·388	vw	2·46	—	—
w	2·290	0·25	2·291	vvs	2·403	0·7	2·39
—	—	0·08	2·234	w	2·301	0·4	2·28
w	2·221	0·08	2·208	vs	1·989	0·8	1·98
s	1·980	0·7	1·982	vw	1·903	—	—
vw	1·890	—	—	vw	1·817	0·2	1·82
vw	1·807	—	—	mw	1·622	0·2	1·62
—	—	0·04	1·732	w	1·578	—	—
—	—	0·04	1·693	vs	1·530	0·5	1·52
w	1·620	0·36	1·619	vvs	1·405	1·0	1·40
w	1·568	0·01	1·586	w	1·302	—	—
s	1·525	0·6	1·527	w	1·256	0·2	1·24
vw	1·473	0·04	1·474	m	1·215	0·2	1·21
vw	1·444	0·05	1·446	m	1·143	0·5	1·14
vs	1·400	1	1·401	m	1·094	—	—
vw	1·343	0·12	1·342	—	—	0·4	1·06
w	1·321	—	—	s	1·033	0·2	1·03
vw	1·300	0·05	1·306	ms	0·992	0·5	0·991
—	—	0·05	1·285	m	0·936	—	—
w	1·255	0·18	1·254	ms	0·916	0·2	0·916
—	—	0·01	1·237	ms	0·887	0·5	0·885
—	—	0·01	1·227	vw	0·871	—	—
w	1·213	0·3	1·209	—	—	—	—
w	1·147	0·23	1·145	—	—	—	—
—	—	0·12	1·112	—	—	—	—
vw	1·062	0·2	1·060	—	—	—	—
w	1·033	0·38	1·032	—	—	—	—
m	0·992	0·3	0·991	—	—	—	—

* Mean of several photographs of good specimens. † After Austin (*loc. cit.*). ‡ After Kordes (*loc. cit.*).

TABLE IV—(*continued*).

Species H.*		Species J (α-spodumene).		Synthetic boehmite.		Boehmite.†	
I.	*d.*	*I.*	*d.*	*I.*	*d.*	*I.*	*d.*
m	9·84	m	6·24	m	7·14	10	6·86
mw	8·39	m	4·46	vs	6·14	10	6·10
w	8·10	m	4·28	w	4·47	—	—
ms	6·68	m	3·49	m	3·52	4	3·53
w	5·33	vw	3·23	vs	3·17	9	3·15
ms	4·88	vw	3·10	vw	2·57	5	2·60
vw	4·55	vs	2·96	vw	2·52	—	—
s	4·27	vs	2·83	w	2·44	—	—
vw	3·97	mw	2·70	vs	2·29	10	2·34
w	3·78	ms	2·48	m	1·98	6	2·04
mw	3·58	m	2·391	vw	1·91	3	1·98
w	3·49	vw	2·200	vs	1·85	10	1·84
mw	3·40	w	2·136	vw	1·82	—	—
mw	3·32	mw	2·085	ms	1·77	4	1·77
vw	3·08	w	2·024	s	1·66	6	1·66
w	2·97	w	1·906	vvw	1·63	2	1·61
w	2·80	vvw	1·869	m	1·53	5	1·53
w	2·66	mw	1·688	mw	1·492	—	—
m	2·52	m	1·623	s	1·452	8	1·45
vvw	2·38	mw	1·594	m	1·432	5	1·433
vw	2·02	w	1·555	vw	1·416	—	—
w	1·87	vvw	1·526	vw	1·402	—	—
		vw	1·502	s	1·383	6	1·380
		w	1·480	vs	1·309	8	1·306
		w	1·351	—	—	1	1·286
		vw	1·332	—	—	1	1·254
		vw	1·302	w	1·225	—	—
		vvw	1·279	w	1·208	2	1·207
		vw	1·234	m	1·176	4	1·176
		vvw	1·217	m	1·156	4	1·158
		vvw	1·193	ms	1·132	6	1·149
		vvw	1·021	mw	1·112	3	1·114
				mw	1·045	3	1·046
				vw	1·037	—	—
				w	1·027	3	1·022
				w	1·010	—	—
				vw	0·991	—	—
				w	0·982	1	0·980
				mw	0·950	5	0·949
				mw	0·930	3	0·931

* "Alphabetical Index of *X*-Ray Data" (American Soc. Testing Materials).
† After Noll (*loc. cit.*).

D are the lithium silicate already described. These crystals appeared in the presence of excess of lithia over the temperature range 200—275°. Table III shows the influence of several variables upon the yields of crystals—variables of pH, temperature, and composition, any of which can exercise a decisive influence on growth of the various species. The figures recorded in Table III are the pH values of the cold mother-liquors after crystallisation; compositions and temperatures are also shown. By keeping the ratio $Li_2O : Al_2O_3 = 1 : 1$, and varying the silica content, a considerable number of crystalline species has, then, been formed under hydrothermal conditions, of which some appear to be new aluminosilicates of lithium. Because of this, considerable attention has been given to their characterisation. Products occurring in major yields of $\geqslant 80\%$ were A, B (α-eucryptite), C (α-petalite), and H, and there is evidence that the species I (β-spodumene) becomes a primary phase above 450°.

Species A (Plate III). *X*-Ray spacings are given in Table IV. The crystals grew as rods up to 30 μ. long, occurring singly and in radial clusters. Birefringence moderate; straight extinction; positive elongation; biaxial; system probably orthorhombic; $\alpha = 1{\cdot}535$, $\gamma = 1{\cdot}525$. Optimum growth: 250° from $Li_2O,Al_2O_3,2SiO_2$ compositions. Addition of small amounts of potassium fluoride had a marked mineralising action. Analysis: Li_2O, 8·30; Al_2O_3, 31·4; SiO_2, 39·8; H_2O, 21·2% ($Li_2O,Al_2O_3,2SiO_2,4H_2O$ requires Li_2O, 9·3; Al_2O_3, 31·5; SiO_2, 37·0; H_2O, 22·2%). This *silicate* exhibits sorptive and ion-exchange properties (*q.v.*).

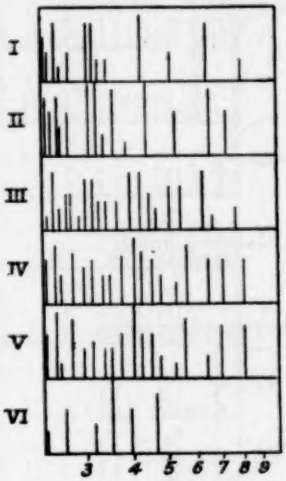
Species B (Plate IV). *X*-Ray spacings (Table IV) identified the mineral as α-eucryptite. The crystals grew as hexagonal prisms occurring singly up to 150 μ. long, and also as radial clusters and spherulites. Cruciform twinning common; birefringent; positive elongation; interference pattern biaxial, therefore pseudo-hexagonal, probably orthorhombic; $\alpha = 1{\cdot}575$, $\beta = 1{\cdot}578$, $\gamma = 1{\cdot}586$. Optimum growth at 400° from $Li_2O,Al_2O_3,2SiO_2$ compositions at pH>10 (excess LiOH, aq.). Analysis: Li_2O, 11·4; Al_2O_3, 40·5; SiO_2, 46·8 (Calc. for $Li_2O,Al_2O_3,2SiO_2$: Li_2O, 11·9; Al_2O_3, 40·5; SiO_2, 47·6%). Crystals were anhydrous and without sorptive or ion-exchange properties. No changes in *X*-ray spacings were apparent after ignition over a Meker burner for 3 hours. Crystallographic pro-

perties are not entirely in agreement with published data (Brush and Dana, *Amer. J. Sci.*, 1880, **20**, 257; Roy, Roy, and Osborne, *loc. cit.*).

Species C (Plate V). *X*-Ray spacings given in Table IV identified the mineral as α-petalite. Crystals grew in prismatic, lath-like, and usually irregular form, both singly and in radial clusters up to 50 μ. long. Low birefringence; straight extinction; positive elongation. Biaxial; mean n 1·510; system monoclinic. Optimum growth at ~420°, from compositions $Li_2O,Al_2O_3,8SiO_2$, at high pH values (excess of LiOH). Analysis: Li_2O, 4·6; Al_2O_3, 16·5; SiO_2, 78·6 (Calc. for $Li_2O,Al_2O_3,8SiO_2$: Li_2O, 4·9; Al_2O_3, 16·7; SiO_2, 78·4%).

FIG. 1.

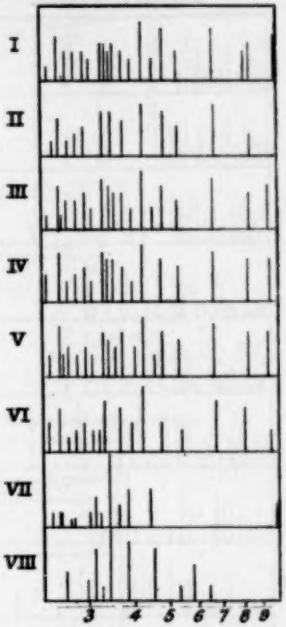
Change in principal lattice spacing on thermal treatment of species A.



I, *Species* A.
II, ,, *heated at* 150°.
III, ,, ,, 200°.
IV, ,, ,, 250°.
V, ,, ,, 360°.
VI, ,, ,, ~800°.

FIG. 2.

Change in principal lattice spacings on thermal treatment of species H.



I, *Species* H.
II, ,, *heated at* 200°.
III, ,, ,, 250°.
IV, ,, ,, 300°.
V, ,, ,, 350°.
VI, ,, ,, 420°.
VII, ,, ,, ~650°.
VIII, ,, ,, ~800°.

(*Horizontal scales in* A. *Vertical distances represent intensities.*)

Species E (Plate VI). Crystals grew as small, yellow-green needles, up to 20 μ. long. High birefringence; straight extinction; positive elongation; mean n ~1·79; probably monoclinic. Growth from $Li_2O,Al_2O_3,3SiO_2$ compositions at ~280°. Reproducibility uncertain. Probably a compound containing iron (from autoclave). Occurs together with species A and B as an alteration product in the hydrothermal recrystallisation of analcite with excess of lithium nitrate at 300°. No major yields obtained, so constitution unknown.

Species F (Plate VII). Formed as hexagonal bipyramids, 25 μ. long. Low birefringence; symmetrical extinction; uniaxial, ε = 1·522, ω = 1·518. System hexagonal. Growth from compositions $Li_2O,Al_2O_3,1$—$4SiO_2$ at 450° and at high pH values. Major yields not obtained, but available data agree with corresponding data for β-eucryptite.

Species G. Small octahedra (~15 μ.). Isotropic; n 1·514. Cubic system. Growth from compositions $Li_2O,Al_2O_3,7SiO_2$, above 450°, and at high pH. No major yield and constitution unknown.

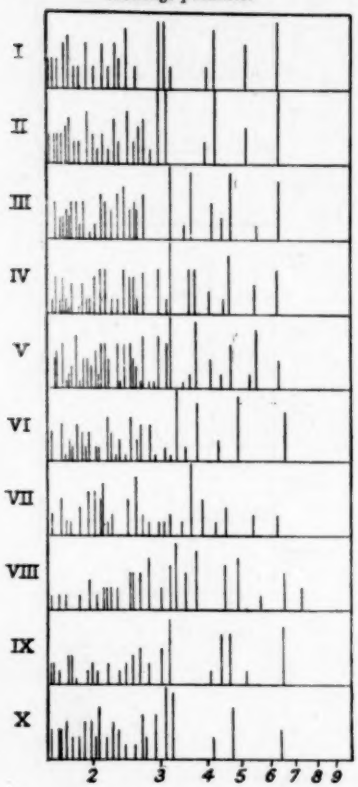
Species H (Plate VIII). *X*-Ray spacings in Table IV. Occurred as rods up to 30 μ. in length, singly and in irregular masses. Birefringence not detectable; n 1·480. System probably tetragonal.

Optimum growth from compositions $Li_2O,Al_2O_3,8SiO_2$ at 220° and with high pH values (excess of LiOH). Analysis: Li_2O, 4·3; Al_2O_3, 14·4; SiO_2, 66·0; H_2O, 13·4% ($Li_2O,Al_2O_3,8SiO_2,5H_2O$ requires Li_2O, 4·3; Al_2O_3, 14·6; SiO_2, 68·4; H_2O, 12·9%). Rarely obtained in yields >80%, but some degree of purification was achieved. This silicate showed ion-exchange and sorptive properties (*q.v.*).

Species I (Plate IX). Prismatic crystals of complex shape, up to 50 μ. long. Birefringence weak, symmetrical extinction; positive elongation; uniaxial; $\omega = 1{\cdot}519$, $\varepsilon = 1{\cdot}524$. Growth from compositions $Li_2O,Al_2O_3,3—8SiO_2$ at 450° and with pH ~10·0. Reproducibility good, but no major yields at 450°. Identified as β-spodumene.

FIG. 3.

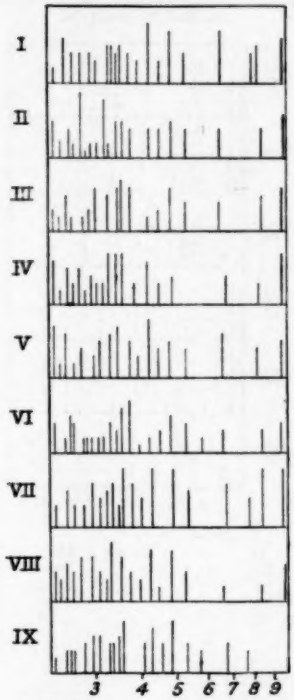
Principal lattice spacings of species A *ion-exchange products.*



I, *Species* A.
II, *Regenerated* Li–A.
III, Na–A.
IV, Ca–A.
V, Ag–A.
VI, K–A.
VII, Ba–A.
VIII, NH_4–A.
IX, Rb–A.
X, Tl–A.

FIG. 4.

Principal lattice spacings of ion-exchange products of species H.



I, *Species* H.
II, Na–H.
III, Ca–H
IV, Ag–H.
V, K–H.
VI, Ba–H.
VII, NH_4–H.
VIII, Rb–H.
IX, Tl–H.

(*Horizontal scales in* A. *Vertical distances represent intensities.*)

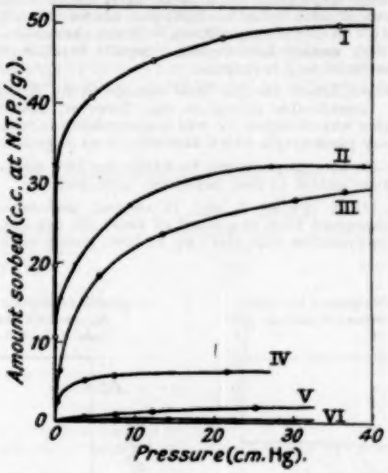
Species J. Lath-like crystals, up to 100 μ. long. Birefringence weak; straight extinction; negative elongation; n ~1·76. Grown from compositions $Li_2O,Al_2O_3,4—8SiO_2$ at ~360°; deposited on stopper and walls of autoclaves, but did not occur in major yields. Identified by *X*-ray data as α-spodumene.

The species A and H were examined further, for thermal stability, ion-exchange, and sorptive properties.

Thermal Stability of Species A *and* H.—Samples of each mineral were heated in air at temperatures between 150° and 450°, in 50° intervals, for about 2 days. The products were cooled in a desiccator

FIG. 5.

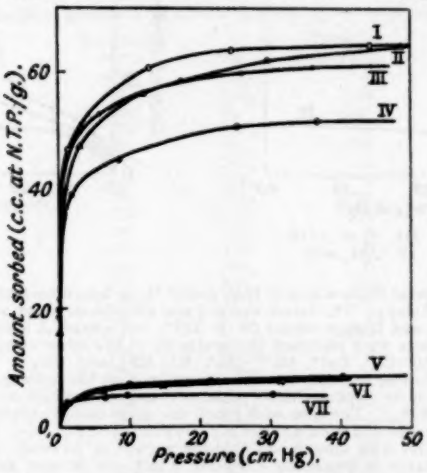
Typical sorption isotherms in species A.



I, NH_3 *at* 0°.
II, NH_3 *at* 0° (*outgassed at* 320°).
III, NH_3 *at* 150°.
IV, N_2 *at* −186°.
V, C_2H_6 *at* 0°.
VI, H_2 *at* −186°.

FIG. 6.

Typical sorption isotherms for species H *and its ion-exchange products.*



Curve no.	*Sorbent.*	*Sorbate.*	*Temp.*
I,	Tl–H	NH_3	0°
II,	Ag–H	NH_3	0°
III,	H	NH_3	0°
IV,	H (*outgassed at* 320°)	NH_3	0°
V,	Tl–H	C_2H_6	0°
VI,	H	C_2H_6	0°
VII,	H	N_2	−186°

and subjected to *X*-ray examination. Irreversible lattice changes were thus detected as changes in *d*-spacings. Finally, specimens were also ignited over Meker burners and re-examined.

Species A, $Li_2O,Al_2O_3,2SiO_2,4H_2O$ (Fig. 1), showed slight lattice changes at 200°, possibly due to loss of water. Further changes were noted at 250°, but above this temperature spacings remained constant until recrystallisation occurred on ignition, without chemical disproportionation. The new species consisted of ill-formed, weakly birefringent, irregular crystals, n 1·522. The *X*-ray powder photograph identified the material as β-eucryptite.

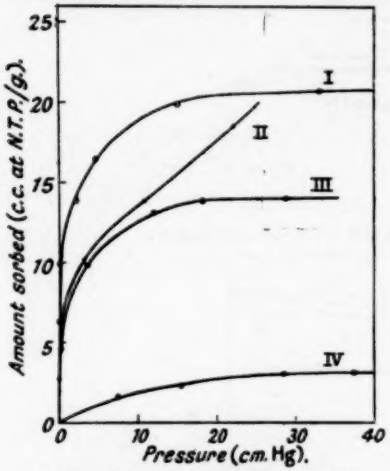
Species H, $Li_2O,Al_2O_3,8SiO_2,5H_2O$, showed little change in its *X*-ray powder photograph up to 350°, when heated in air. Considerable alteration was, however, observed at 430°. On ignition, a solid of amorphous appearance was obtained; it was homogeneous as regards refractive index (n 1·524) and gave a well-defined *X*-ray photograph which identified it as β-spodumene.

These experiments indicate the temperatures to which the two minerals may safely be subjected during outgassing, before investigation of their behaviour as sorbents.

Ion-exchange Reactions.—Both species A and H showed well-defined ion-exchange properties. Species B, which was also examined from this point of view, did not undergo ion-exchange. Both A and B, however, tended to recrystallise with NaCl,aq. at 150°, giving analcite, $Na_2O,Al_2O_3,4SiO_2,2H_2O$.

FIG. 7.

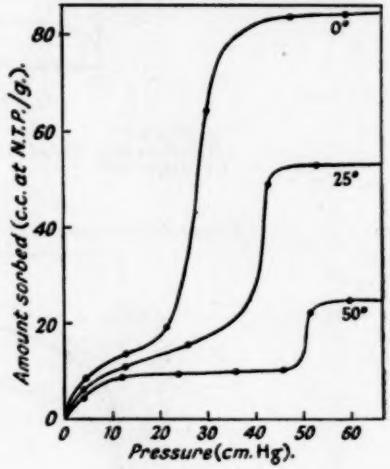
Some typical isotherms in an outgassed but otherwise untreated lithium aluminosilicate gel ($Li_2O,Al_2O_3,3SiO_2$).



I, NH_3 *at* 0°. III, N_2 *at* −186°.
II, NH_3 *at* 50°. IV, C_2H_6 *at* 0°.

FIG. 8.

Sigmoid isotherms obtained with NH_3 *on species* A, *converted into* Ag–A *and then reconverted into* A *by ion-exchange* $Li^+ \rightleftharpoons Ag^+$.



Silver ions readily replaced lithium ions in both A and H, on hydrothermal treatment with excess of silver nitrate at 110° for 2 days. The fusion method also introduced silver and barium ions on use of silver nitrate (m. p. 212°) and barium nitrite (m. p. 217°), but species A showed some decomposition. Other ion-exchange products were obtained by treatment of the silver compounds with solutions of metallic chlorides at ~110° (Tl^+, Ca^{++}, Ba^{++}, Na^+, K^+, Rb^+, and NH_4^+). Most of these exchange products were then entirely free from silver ions. However, with the ammonium compounds, whether prepared hydrothermally or by vapour-phase exchange (using ammonium chloride vapour), there was only limited exchange (~10%). The ease with which the silver cation exchanged forms were made is in accordance with the behaviour of some zeolites (*e.g.*, Taylor, *Proc. Roy. Soc.*, 1934, **145**, *A*, 80; Barrer, *J.*, 1950, 2342). The result with ammonium chloride vapour is, however, in contrast to the usual behaviour where ion exchange is frequently extensive (Clark and Steiger, *loc. cit.*; Barrer, *J.*, 1948, 2158; *loc. cit.*).

From crystals of Ag^+–A, treatment with excess of lithium chloride gave the species A with only minor difference in the *X*-ray powder photographs from the original sample of A, although the sorptive properties (*q.v.*) indicated that a change had occurred. In general, changes in both intensities and spacings were, however, apparent among the ion-exchanged forms (Figs. 3 and 4). Exchange was also followed by measurements of refractive indices, which were considerable for silver and thallous compounds. The birefringence in most cases decreased, exceptions being silver and thallous ion exchanged forms. Partial analyses of products were made to determine the degree of exchange, calculations being based on the formula $(R'', R'_2)O,Al_2O_3,2SiO_2,4H_2O$.

The species H could not be regenerated from its silver ion exchanged form by hydrothermal treatment with excess of lithium chloride or by fusion with lithium nitrate. Exchange was sometimes accompanied by increases in refractive indices, but not to the same extent as with the mineral A, and all products were isotropic. *X*-Ray diffraction patterns showed changes in intensity, but the spacings were constant within errors of measurement (Fig. 4). Specimens of H used in the ion-exchange experiments were not so pure as those of A, small amounts of unchanged gel being present in most cases. Partial analyses for the ion-exchanged products are therefore of uncertain value and are omitted. The presence of the exchanged ions was, however, demonstrated by analysis. Some ion-exchange data for both species are given in Table V.

TABLE V.

Ion-exchange data for species A *and* H.

Exchange cations.	Species A. R.I. (mean).	Species A. Exchange, %.	Species H.† R.I.
Li^+ (original)	1·53	—	1·48
Li^+ (regenerated from Ag^+–A)	1·53	100 *	—
Na^+	1·54	33·8	1·49
Ca^{++}	1·56	12·0	1·49
Ag^+	1·66	88·1	1·54
K^+	1·54	28·1	1·49
Ba^{++}	1·55	85·6	1·49
Tl^+	1·70	79·5	1·54
Rb^+	1·55	—	1·49
NH_4^+	1·54	11·1	1·49

* On basis of complete absence of Ag^+.
† Products and parent mineral isotropic; $Li^+ \longrightarrow Ag^+$ not reversible.

Sorptive Properties of A *and* H.—Several samples of A and H were tested as sorbents together with some cation-exchanged forms of these minerals, and a specimen of untreated dry gel of composition $Li_2O,Al_2O_3,3SiO_2$. The maximum amounts of several gases sorbed in our experiments are given in Table VI, and a number of characteristic isotherms in Figs. 5, 6, 7, and 8.

TABLE VI.

Sorptive behaviour of several lithium aluminosilicates.

Specimen.	Outgassing temp.	Gas.	Temp. of isotherm.	Max. sorption, obs., c.c. at N.T.P./g.	
A	220°	NH_3	0°	50	
	220	NH_3	150	30	
	220	N_2	−186	6·5	
	220	C_3H_8	0	2·0	
	220	H_2	−186	0·3	
	300	NH_3	21	3·3	
Regenerated Li–A	230	NH_3	0	84	
	230	NH_3	25	53	
	230	NH_3	50	25	
Ba–A	230	NH_3	0	~ 5·0	
Ag–A	230	NH_3	0	~ 6·0	(not true equilibrium)
	230	NH_3	0	2·0	
	230	NH_3	50	3·7	
	230	NH_3	100	~15	
H	230	NH_3	0	60	
	230	N_2	−186	5·4	
	230	C_3H_8	0	7·8	
	320	NH_3	0	52	
Ag–H	230	NH_3	0	65	
Tl–H	230	NH_3	0	65	
B	240	NH_3	0	3·2	
Gel $Li_2O,Al_2O_3,3SiO_2$	230	NH_3	0	21	(saturation not reached)
	230	NH_3	50	18·5	
	230	N_2	−186	14·2	
	230	C_3H_8	0	3·1	

The mineral A showed a moderate capacity to occlude ammonia at 0°, but uptake of propane at 0° and of nitrogen at −186° was limited. The behaviour of Ag^+–A was unusual; the crystals occlude more ammonia above 0° than at this temperature, so it is probable that intracrystalline diffusion of ammonia sets in freely only at higher temperatures, and isotherms do not represent true equilibrium. Similar behaviour has frequently been observed with zeolitic crystals, where activated diffusion may be very slow at lower temperatures (*e.g.*, Barrer, *Trans. Faraday Soc.*, 1949, **45**, 363). It is also found in crystals where the lattice is subject to expansion and contraction according to the content of inter-

stitial water or other small polar molecules. Examples include fibrous and laminar zeolites such as natrolite and heulandite (Barrer, *Proc. Roy. Soc.*, 1938, *A*, **167**, 392, 406). The regenerated Li^+–A produced sigmoid ammonia isotherms (Fig. 8), the initial portion being largely due to sorption on external, easily accessible surfaces which become saturated. After an approximate threshold pressure, however, penetration began, with an approach to saturation of intracrystalline sorption sites at higher pressures. This behaviour is closely analogous to that observed in the ammonia–natrolite system (Barrer, *loc. cit.*), and is again indicative of a collapsing and expanding lattice. Outgassing of specimens above 250° seriously impaired the sorptive behaviour of the crystals.

Crystals of the species H also showed a considerable sorptive power towards ammonia. Base exchange ($Li^+ \rightleftharpoons Ag^+ \rightleftharpoons Tl^+$) did not alter this affinity very greatly (Table VI), and no anomalous effects characteristic of a swelling and shrinking lattice were observed. This contrast between A and H is entirely in accord with their lattice stabilities deduced from structural changes on ion-exchange and on thermal treatment. Specimens of H outgassed at 320° were not quite as active as those outgassed at ~220°, but the decrease was less marked than for species A.

The sorption of ammonia by the anhydrous species B was confined to a small amount of adsorption upon external surfaces of the crystallites. No evidence of intracrystalline sorption was obtained. Ammonia was, however, sorbed to a considerable extent by a sample of outgassed uncrystallised gel, though not so much as by species A and H (Table VI). At −186° nitrogen was, as might be expected, rather more strongly adsorbed on the gel than on the crystalline materials. However, since the samples of A and H used approached 100% purity, the sorption there observed cannot be ascribed to the presence of amorphous gel.

Discussion.

The species A and H have the ratios $Li_2O : Al_2O_3 = 1 : 1$, contain crystal water replaceable by ammonia to give continuous sorption isotherms, and show ion-exchange properties. In all these ways they conform to the definition of a zeolite, and it is thus possible that two entirely synthetic new zeolites have been prepared. Of these species, one (mineral A) shows a tendency to lattice changes, partially reversible, on outgassing or ion exchange, and is to be compared therefore with the fibrous or laminar zeolites (*e.g.*, the natrolite group and heulandite). The other species (mineral H) is less prone to these lattice changes, and may be likened more nearly to the robust three-dimensional network zeolites (chabazite, gmelinite, analcite, harmotome, mordenite, or levynite).

This work has largely been carried out in a temperature range complementary to that investigated by Roy, Roy, and Osborne (*loc. cit.*), where crystallisation was studied mainly above 450°. Results are in good agreement, except for the formation of β-eucryptite at temperatures of *ca.* 450°; also the inversion of α-petalite to β-eucryptite was not observed on several hours' heating at ~800°.

There are interesting differences in physical properties between natural and synthetic α-eucryptites. As between synthetic and natural specimens, one finds appreciable variations in refractive indices, the synthetic crystals (this paper; and Roy, Roy, and Osborne, *loc. cit.*) having higher values of n than natural crystals (Brush and Dana, *loc. cit.*). There are also apparent variations in crystal habit and system between the synthetic minerals obtained by ourselves and by Roy, Roy, and Osborne. On the other hand, the *X*-ray photographs of both sets of synthetic crystals agree excellently *inter se* and with those of naturally occurring α-eucryptite.

α-Spodumene occurred only as a deposit on autoclave walls, considerably contaminated with ferric oxide; *X*-ray data were, however, obtainable and gave positive identification. Again, refractive indices were considerably in excess of values quoted for the natural mineral but were in better agreement with those for synthetic α-spodumene grown by Roy, Roy, and Osborne (*loc. cit.*).

As would be expected from the high density and refractive index of α-spodumene, this mineral was produced only at ~400°, and in small quantities. Species A and H, the open zeolitic crystals with a considerable content of water molecules, were, on the other hand, produced at low temperatures (Table III). The formation of β-spodumene and β-eucryptite would appear analogous to the hydrothermal formation of metastable cristobalite (*e.g.*, Wyart, *Bull. Soc. franç. Min.*, 1943, 479; H. F. W. Taylor, *J.*, 1949, 1253), when the stable phase (α-quartz) would be expected.

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Marischal College, Aberdeen. [*Received, December 4th*, 1950.]

284. *Amino-acids and Peptides. Part III. The Solubility Criterion of Chemical Purity with Special Reference to Amino-acids. The Use of Differential Vapour-pressure Measurements.*

By I. W. Hughes, E. W. Williams, and G. T. Young.

The solubility of a pure substance is independent of the amount of excess solute present, and this " solubility criterion " of purity is of great value for substances for which more normal criteria are inapplicable. The use of a direct differential procedure for detecting differences in solubility offers many advantages, and in this paper a method is described in which differential vapour-pressure measurements are used to detect small amounts of impurities in materials such as amino-acids. The limitations of the method are discussed.

During work on the isotope dilution method of amino-acid analysis, we have encountered the difficulty of establishing the purity of the sample isolated, on which the accuracy of the determination depends. Observation of the sharpness of melting point is of little value for amino-acids and, since the contaminants may be of closely similar composition or even isomeric, elementary analysis is of limited use. In such cases, a valuable criterion has been derived from the fact that the solubility of a pure substance is independent of the amount of excess solute present; this has been used to examine the homogeneity of proteins (Kunitz and Northrop, *J. Gen. Physiol.*, 1930, **13**, 781; Butler, *ibid.*, 1940, **24**, 189) and of amino-acids (Dunn, Frieden, Stoddard, and Brown, *J. Biol. Chem.*, 1942, **144**, 487). In these cases, conventional methods for solubility determination were applied.

It is not, however, necessary to obtain absolute measurements for this purpose and differential procedures present many advantages. An interesting approach was that by Halford (*J. Amer. Chem. Soc.*, 1931, **53**, 2640) who observed the elevation in boiling point of successive saturated extracts of the substance to be examined. We have developed a method, suitable for use with materials of relatively low molecular weight, by which the difference in solubility is detected by a direct comparison of the vapour pressures of the solutions. Essentially, two saturated solutions are prepared, one containing the minimum excess of solute and the other a large excess; the difference in vapour pressure is then observed by means of a differential tensimeter. A preliminary note (Hughes and Young, *Nature*, 1949, **164**, 503) reported this development and its use in establishing the purity of amino-acids. In this way it is possible to detect contamination by enantiomorphs, and proof of identity, analogous to that by mixed melting point determinations, may also be obtained. We now describe fully the apparatus and procedure, and present the results of a more detailed examination of the sensitivity of the method in certain cases.

Properties other than vapour pressure may, of course, be used as the basis of a differential solubility test. Since the publication of our note, the use of radioactivity measurements for this purpose has been described (Gutmann and Wood, *Science*, 1949, **110**, 662). We have developed an alternative general method, in which the refractive indices of the solutions are compared. This will be described later.

The sensitivity of the vapour-pressure method under typical conditions has been determined for three series of mixtures, consisting of known amounts of (*a*) potassium nitrate in " AnalaR " sodium chloride, (*b*) DL-alanine in " AnalaR " glycine, and (*c*) L-aspartic acid hydrochloride in L-glutamic acid hydrochloride. The results are shown in Figs. 1—3. Over the range of concentration investigated and under the conditions specified in the Experimental section, the difference in vapour pressure is proportional to the amount of impurity present, and in each case *ca.* 0·2% of the contaminant was readily detected.

In the preliminary work (Hughes and Young, *loc. cit.*), we had difficulty in obtaining a satisfactory sample of glycine; during the present work several samples of " AnalaR " glycine were examined and each appeared to be of high purity.

The Significance and Sensitivity of the Differential Solubility Test.—The application of the solubility criterion of purity to proteins has been discussed by Kunitz and Northrop and by Butler (*locc. cit.*). In brief, the observation that the solubility is independent of the amount of excess solid leads to the deduction from the phase rule that the number of components (including the solvent) is equal to the number of phases; any number of insoluble components might

therefore be present. In practice, such a test is normally applied to materials purified by repeated crystallisation, and the contaminants are likely to be of similar solubility. In order to be able to deduce from this test that the sample is pure, it is however essential that the smaller excess of solid should consist of a single phase, and for this reason emphasis is laid on the use of the minimum excess of solid in one vessel. If two substances are present in amounts exactly proportional to their solubilities, they will behave for this purpose as one component; impurity

FIG. 1.

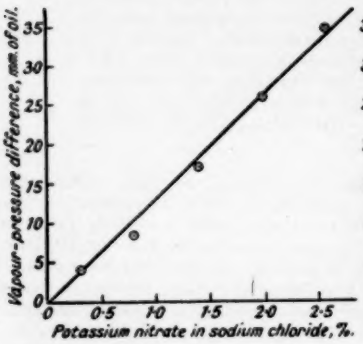


FIG. 2.

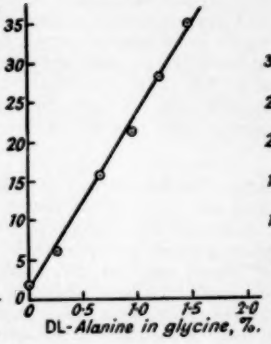


FIG. 3.

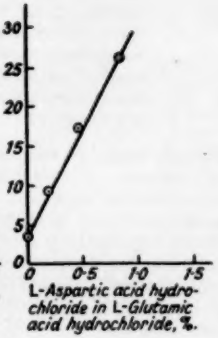
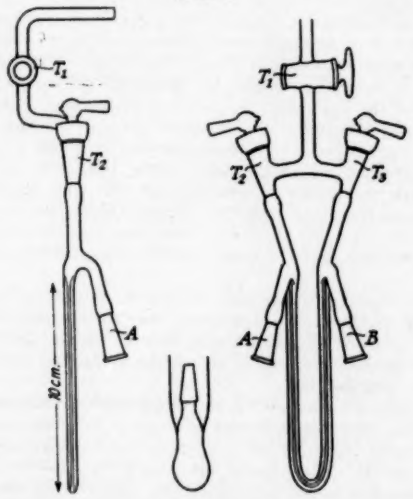


FIG. 4.



should however be detected by changing the temperature or by examination in a second solvent; in either case it is unlikely that the solubilities will change in the same proportion. In the case of solid solutions, equilibrium with the solvent may be difficult to establish, but unless again the substances are present in the same ratio as their solubilities, the criterion should be applicable. It must be noted that contamination by the solvent in which the test is made will not be detected.

The sensitivity of the method depends on the difference in concentration of the impurity in the two solutions. With purified materials, this concentration will be low in one solution, whereas in the other the amount of solid may be increased until the solution is saturated both

with the main component and with the impurity. The greatest sensitivity may therefore be expected when the solubility of the impurity is high. The sensitivity clearly depends also on the molecular weight of the impurity; small amounts of macromolecules would not be detected by the present method. The use of higher temperatures will also increase the sensitivity, but practical difficulties, such as the prevention of leaks, also become greater.

The use of the differential vapour-pressure test is not, of course, restricted to the examination of amino-acids, and it may be found of value for the establishment of the purity or of the identity (Hughes and Young, *loc. cit.*) of many other types of substance to which more normal criteria are inapplicable.

Experimental.

Apparatus.—The apparatus, of Pyrex glass, is drawn to scale in Fig. 4. The U-tube manometer is of uniform capillary tubing, 1·5 mm. in diameter. Taps T_1 and T_2 are right-angled, with mercury seals. Two small vessels (volume *ca.* 2 ml.), which contain the solutions, have B.10 "Quickfit" cones (ground further if necessary) to fit sockets *A* and *B*; these vesels also are provided with mercury seals. It is advisable to keep the volume of the apparatus as small as practicable, to diminish the effect of slight differences in the temperature of the arms. For the same reason, the apparatus is so constructed that the vessels are as close to each other as possible, lying immediately behind the manometer. For the taps and joints, we have found "Silicone" grease satisfactory, provided that it is thoroughly removed after each experiment. The apparatus is supported in a glass-walled thermostat bath maintained at 50° ± 0·1°; the barrels, but not the handles, of taps T_1 and T_2 are immersed. We have found Apiezon Oil C (d^{20}, 0·80) a more satisfactory manometer fluid than the xylene mentioned in our preliminary note. The difference in level of the oil in the two arms was measured sufficiently accurately for the present work by means of a graduated scale mounted behind the manometer.

Method.—The following procedure is typical of that adopted to examine the purity of a substance, when using aqueous solutions and a temperature of 50°.

Into one vessel is weighed just sufficient of the material to saturate 0·1 ml. water and to leave a visible excess, and approx. ten times this weight is placed in the second vessel; water (0·1 ml.) is then added to each. It is helpful to mix the solvent and solute with a thin glass rod. The joints are carefully greased and both vessels attached firmly to the apparatus, all taps being open. Mercury is placed in the seals and the apparatus is transferred to the thermostat. After some minutes (to allow the air to expand) tap T_1 is closed, and then taps T_3 and T_4. After several hours, when considerable dissolution has occurred, the attainment of equilibrium in the two solutions may be hastened by reducing the pressure gradually to *ca.* 10 cm., by connecting T_1 to a water-pump (provided with a manometer and air-leak), with T_3 and T_4 open. The taps are then immediately closed in that order. The manometer liquid may again require levelling at intervals by opening and closing taps T_3 and T_4.

We have usually found that saturation is reached within 24 hours, after which the apparatus is re-evacuated to *ca.* 10 cm. pressure as before. Tap T_1 is closed and the manometer liquid should then be level in both arms. Taps T_3 and T_4 are now closed. The manometer level should become steady in about an hour, and the difference in height is noted. The evacuation and subsequent procedure is repeated after a further hour, until the pressure difference is reproducible to within 1 mm., indicating that equilibrium has been attained.

It is advisable to test new apparatus by carrying through similar operations with both vessels empty, in order to detect leaks. It is, of course, essential that, when the final reading is taken, no pure solvent should be present in any part of the system; this should not occur if the apparatus is adequately immersed and if equilibrium has been reached. It is often desirable to carry out the final recrystallisation with the solvent to be used in the vapour-pressure test; traces of residual solvent will not then affect the observations.

Examination of Synthetic Mixtures.—Three series of mixtures were prepared: (*a*) potassium nitrate in "AnalaR" sodium chloride, (*b*) DL-alanine in "AnalaR" glycine, and (*c*) L-aspartic acid hydrochloride in L-glutamic acid hydrochloride; the percentage compositions and vapour-pressure differences (expressed in mm. of Apiezon Oil C) are shown in Figs. 1—3. In each experiment, one vessel contained 0·1 g. of mixture and the other 1·0 g.; 0·1 g. of water was added to each. The temperature of the thermostat was 50°.

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285. *The Decomposition of Primary Nitramines in Alkaline Solutions.*

By J. Barrott, M. I. Gillibrand, and Alex. H. Lamberton.

Primary nitramines have generally been considered to be stable towards aqueous alkalis. It has now been found that, in a number of instances, the reaction $RR'CH{\cdot}NH{\cdot}NO_2 \longrightarrow RR'C{=}O + N_2 + H_2O$ occurs on heating in presence of an excess of aqueous sodium or potassium hydroxide. The reaction is not simply the thermal decomposition of the nitramine anion and, though undoubtedly complex, it is often pseudo-unimolecular. It appears to be favoured by (*a*) increasing concentration of hydroxyl ions, (*b*) increasing concentration of sodium or potassium ions, and (*c*) increasing electron-attractive power of the groups R and R'. As the equation indicates, the presence of a hydrogen atom on the α-carbon is apparently essential.

Van Erp (*Rec. Trav. chim.*, 1895, **14**, 45) found that the anions of simple aliphatic nitramines were not attacked by hot 20% aqueous potassium hydroxide. His observations, together with the use of nitramine salts in preparative work, led to the assumption that all primary nitramines showed considerable stability towards aqueous alkalis. This statement must now be qualified.

Hantzsch and Metcalf (*Ber.*, 1896, **29**, 1680) found that nitraminoacetic acid (I; R = H, R' = CO_2H) was decomposed, with the evolution of nitrogen, by treatment with sodium hydroxide. J. K. N. Jones (private communication) observed that methylenedinitramine was readily decomposed by an excess of caustic alkali; and the existence of a zone of comparative stability around pH 10 suggested that the reaction was not the same as that (around pH 5) previously investigated in some detail (Lamberton, Lindley, and Speakman, *J.*, 1949, 1650). Furthermore, the gas evolved from methylenedinitramine in 1·0M-potassium hydroxide has been found to contain both nitrous oxide and nitrogen: the evolution of nitrogen is not typical of nitramine decompositions which have hitherto been recognised.

$RR'CH{\cdot}NH{\cdot}NO_2$ (I.)

p-$CHO{\cdot}C_6H_4{\cdot}N{:}N{\cdot}C_6H_4{\cdot}CHO$-$p$ (II.)

We have confirmed the production of nitrogen from nitraminoacetic acid, and also examined its ethyl ester (I; R = H, R' = CO_2Et), whose stability as a nitramine was not investigated by Hantzsch. The ester was found by us to decompose much more readily than the acid, nitrogen being evolved with moderate rapidity on heating of solutions of as low a pH as 6·8; and at pH 8·7 hydrolysis was marked by the cessation of gas evolution as the residual ester was converted into the more stable acid. If, as seems likely, the first dissociation constant of nitraminoacetic acid represents the ionisation of the carboxyl group, then the change from ester to acid at pH 8·7 is in fact the replacement of CO_2Et by CO_2^-. The carbethoxyl group is more electron-attractive than the ionised carboxyl group (a statement borne out, incidentally, by a comparison of the dissociation constant of nitraminoacetic ester with the second dissociation constant of the acid), and it was tentatively assumed that electron-attractive groups facilitated the decomposition.

On this hypothesis, and to isolate more easily the non-gaseous reaction products by the use of a nitramine of higher molecular weight, p-nitrobenzylnitramine (I; R = H, R' = p-$NO_2{\cdot}C_6H_4$) was next examined. It decomposed readily in the presence of excess of alkali, but secondary reactions also occurred: thus when a 0·1M-solution of the sodium salt in 0·1M-sodium hydroxide was heated the azoxyaldehyde (II) was precipitated in 62% yield (on basis 2 molecules nitramine ⟶ 1 molecule dialdehyde). In other respects, also, the behaviour of p-nitrobenzylnitramine appeared to be unusual, and has not been fully investigated.

$(p\text{-}C_6H_4R)_2{\cdot}CH{\cdot}NH{\cdot}NO_2$ (III.)

p-$C_6H_4R{\cdot}CHMe{\cdot}NH{\cdot}NO_2$ (IV.)

In order to avoid secondary reactions associated with *C*-nitro-groups, we turned to the diphenylmethylnitramines. Though showing greater stability, they were completely decomposed—in periods varying from a few hours to a few days—in aqueous 1·0M-potassium hydroxide

at 95°. Diphenylmethylnitramine (III; R = H) and its 4 : 4′-dibromo-, 4 : 4′-dimethyl-, and 4 : 4′-dimethoxy-derivatives have been examined. In order to elucidate the reaction, comparable experiments have been made using methyl-, phenyl-, benzyl-, 1-phenylethyl- (IV; R = H), and 1-*p*-bromophenylethyl-nitramine (IV; R = Br).

The corresponding ketones (*e.g.*, benzophenone from III; R = H) have been obtained in good yield by complete decomposition of the diphenylmethylnitramines. Benzaldehyde (as the 2 : 4-dinitrophenylhydrazone) and benzoic acid (presumably as the result of a Cannizzaro reaction) have been obtained from the unstable benzylnitramine. 1-Phenylethyl- and 1-*p*-bromophenylethyl-nitramine could not be completely decomposed in a reasonable time, even by means of stronger (*e.g.*, 4M-)potassium hydroxide; but acetophenone and *p*-bromoacetophenone have been isolated, as 2 : 4-dinitrophenylhydrazones, after partial decomposition of these nitramines. Phenylnitramine was stable, and recoverable. No attempt was made to isolate the decomposition products of methylnitramine. In most cases the gas evolved was tested, qualitatively, for (water-soluble) nitrous oxide: none was observed. A gas sample from diphenylmethylnitramine was collected with complete exclusion of air, and was found by analysis to consist solely of nitrogen. It thus appears that the overall decomposition is

$$>CH\cdot\overset{\ominus}{\overbrace{N\cdot NO_2}} \longrightarrow >C{=}O + N_2 + \overset{\ominus}{O}H \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

though it must be emphasised that an excess of alkali is required, and the process is not simply the thermal decomposition of the nitramine ion.

The progress of decomposition has been followed by measurement of the gas evolved. The total volume of gas produced from benzylnitramine, and from the various diphenylmethylnitramines, corresponded closely with that expected on the basis of equation (1); and the validity of the measurements was further established by the recovery and determination, in a few cases, of the residual nitramine after partial decomposition had taken place. The validity of gas evolution as a measure of the decomposition of methylnitramine, and of the phenylethylnitramines (IV; R = H or Br), has been assumed, though not strictly proven.

TABLE I.

Decomposition of potassium salts of the nitramines R·NH·NO_2, *initially* 0·05M., *in aqueous* 1·0M-*potassium hydroxide at* 95°.

Run nos.	R.	Apparent first-order constant, 10^4k min.$^{-1}$, at residual concentration of nitramine salt: 90%.	65%.	40%.
I, XIII	Me	0·6	—	—
II	Ph	Stable [1]	—	—
III	Ph·CH_2	640	640	640
XLIV	Ph·CHMe	Stable [1]	—	—
XLV, XLVI	*p*-C_6H_4Br·CHMe	Stable [1]	—	—
VI, VII, XIV, XV, XVI	Ph_2CH	16·6	16·6	16·6
XI, XII, XXII	$(p\text{-}C_6H_4Br)_2CH$	77	105	135
IX, XVII, XVIII	$(p\text{-}C_6H_4Me)_2CH$	3·7	4·6	4·9
X, XXI	$(p\text{-}MeO\cdot C_6H_4)_2CH$	2·4	2·4	—

[1] Measurable rates of reaction (see Experimental section) were observed in more concentrated (4M- and 8M-)potassium hydroxide. In the case of phenylnitramine the extremely slow decomposition was clearly of a quite different (oxidative?) type, since it led to a reduction in the volume of the enclosed gas.

Though the overall decomposition presumably represents the summation of several reactions, there often appeared to be a rate-determining step, and the decomposition was then of the first-order with respect to the nitramine. In the case of diphenylmethylnitramine, the individual decompositions showed a close correspondence with the first-order reaction-rate law under a variety of conditions. In other cases, notably di-(*p*-bromophenyl)methylnitramine, the first-order rate "constant" increased as decomposition progressed. The relative stability of the potassium salts of various nitramines in 1·0M-potassium hydroxide at 95°, and the variation of the apparent, instantaneous, first-order constants (obtained from graphs of log residual concentration of nitramine against time), are given in Table I. The small increase in free-alkali content during decomposition (equation 1) is not sufficient to produce a significant change in rate.

Factors affecting the Rate of Reaction.—(a) *Environmental.* Diphenylmethylnitramine was examined under a variety of conditions, and the (first-order) rate of decomposition was found

to depend both on the concentration, and on the nature, of the alkali employed. Inspection of Table II shows that, for constant [OH], the rates were proportional to 0·66[Na] and to 0·75[K]. It may be that, if strictly relevant values were known, these variations could be accounted for in terms of the activity coefficients of the ions involved. On the other hand, it appeared, quite empirically, that cationic concentration, rather than " total ionic strength " was the determining factor: thus the presence of M-potassium chloride had quantitatively the same effect as M/3-, not M/6-potassium phosphate; and the nature of the anion seemed to be irrelevant. If allowance was made for the changes in [Na] and in [K], then the rates were proportional, in both hydroxides, to 1·1[OH].

The quantitative significance of these results for other compounds is doubtful. Though a two-fold increase in the concentration of potassium hydroxide brought about a 3·2-fold increase in the rate of decomposition of diphenylmethylnitramine, the corresponding ratios for benzylnitramine and di-*p*-tolylmethylnitramine were *ca.* 2·5 and 1·8.

(b) *Structural.* It appears that the presence of a hydrogen atom on the α-carbon is essential. It is removed in the formation of the ketone (or aldehyde), and when it does not exist (phenylnitramine) stability ensues. An aromatic nitramine, however, cannot be regarded as strictly analogous to the other compounds investigated, and it is hoped to give further consideration to this question.

We have attempted to relate stability to the electron-attractive character of the groups (I; R and R′) attached to the α-carbon of the various nitramines. This property has been measured by the determination of dissociation constants. In view of the different conditions employed in the measurement of stability and of acidity, a quantitative correspondence was not expected; but it was found that, in the case of the closely-related diphenylmethylnitramines, there was some degree of parallelism (as illustrated in Fig. 1) between acidity and rate of decomposition. The relationship was dubious when applied to the unexpectedly stable phenylethylnitramines, and failed in the cases of benzylnitramine and *p*-nitrobenzylnitramine; it may well fail also [see conclusion of section (a), above] when considerable changes are made in the concentration of alkali employed. It does, however, appear that, other factors being equal, the more acidic of a pair of nitramines is likely to exhibit also the faster decomposition.

TABLE II.

Decomposition of alkali-metal salts of the nitramines, R·NH·NO_2, *initially* 0·05M. *in various solvents, at* 95°.

Run nos.	R.	Solvent.	First-order rate constant, 10^4k, min.$^{-1}$.
VIII	Ph_2CH	0·5M-KOH	5·6
VI, VII, XIV, XV, XVI	"	1·0M-KOH	16·6
V, Va, XL	"	2·0M-KOH	53·4
XXXIV, XXXV	"	1·0M-KOH + 1·0M-KCl	23·2
XXXVI	"	" + 0·5M-K_2CrO_4	24·4
XXXVII, XXXVIII	"	" + 0·16M-K_3PO_4	18·6
XXXIX	"	" + 0·33M-K_3PO_4	24·1
XXVIII, XXIX	"	1·0M-NaOH	13·0
XXXII, XXXIII	"	2·0M-NaOH	38·1
XXX	"	1·0M-NaOH + 1·0M-NaCl	16·9
XXXI	"	" + 0·5M-Na_2SO_4	17·3
IV	$PhCH_3$	0·5M-KOH	260
III	"	1·0M-KOH	640
IX, XVII, XVIII	$(p\text{-}MeC_6H_4)_2CH$	1·0M-KOH	3·7 (90%) to 4·9 (40%)
XIX	"	2·0M-KOH	6·2 (90%) to 9·0 (40%)

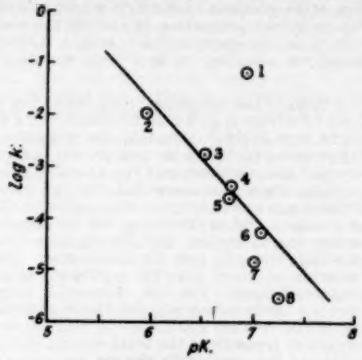
We do not postulate, with conviction, any definite reaction mechanism; but some tentative suggestions may be made. The importance of alkali concentration lies possibly in the removal of the α-hydrogen atom as a proton. Sodium and potassium cations facilitate the decomposition, and, unless this is simply an activity-coefficient effect, it might be inferred that the proton is removed from the small proportion of undissociated salt, rather than from the nitramine anion. Alternatively, the proton may shift, by changing a hydrogen bond * into a normal linkage, to an oxygen of the nitro-group; and the importance of hydroxyl-ion concentration may lie in the attack, at a later stage, on the C=N double bond.

* We are indebted to Professor E. L. Hirst for the suggestion of hydrogen bonding: the C–O distance is probably (from the work of Llewellyn and Whitmore, *J.*, 1948, 1316) about 2·7 A.

By what are essentially anionic migrations, the hybrids (V, VI) might yield structure (VII), and a repetition of the process would give the ketone (in hydrated form) and nitrogen. It may be contended that the oxygen atoms could not readily be removed from the nitro-group in the

FIG. 1.

Relation between observed first-order constant of decomposition (k, *min.*$^{-1}$) *and acidity* (pK)



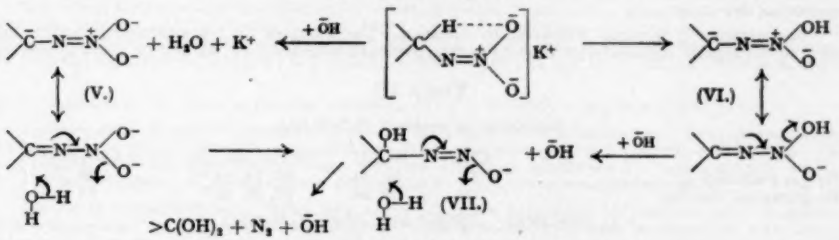
M/20-*solutions of*:

(1) Ph·CH_2·NH·NO_2.
(2) (p-C_6H_4Br)$_2$CH·NH·NO_2.
(3) Ph_2CH·NH·NO_2.
(4) (p-C_6H_4Me)$_2$CH·NH·NO_2.
(5) (p-MeO·C_6H_4)$_2$CH·NH·NO_2.
(6) Me·NH·NO_2.
(7) p-C_6H_4Br·CHMe·NH·NO_2. } *Estimated, very roughly, as* $\frac{1}{10}$*th of the*
(8) Ph·CHMe·NH·NO_2. } (*observed*) *values in* 4M-KOH.

In 1·0M-KOH *at* 95°.

In cases of variation of the "constant" during decomposition, the observed value at 65% *residual nitramine has been used.*

form of hydroxyl ions; but this must ultimately be the fate of at least one of them, and the formation of molecular nitrogen provides a powerful driving force.



EXPERIMENTAL.

Decomposition of Nitraminoacetic Acid, and of its Ethyl Ester.—One molecular proportion of gas was evolved, in a closed system, when the acid was heated with a large excess of 1·0M-sodium hydroxide, and the ester with a phosphate buffer (2M-H_3PO_4; 2M-NaOH) at pH 7. A sample of the gas evolved appeared in both cases to be wholly insoluble in cold water. The rates of decomposition at 70° were measured, by gas evolution, as previously described (*J.*, 1949, 1654); and the results may be briefly summarised. M/20-Solutions of both ester and acid were used; the phosphate buffers were made from 1·0M-phosphoric acid and 1·0M-sodium hydroxide. Both compounds were stable in 1·0M-nitric acid, and at pH 2·8. The acid was stable, or nearly so, at pH 5·4 and 6·5; it decomposed slowly (13% in one hour) at pH 10·6, and rapidly (complete in 10 minutes) in 1·0M-sodium hydroxide. The ester decomposed slowly, and with moderate speed (15 and 40%, respectively, in 1 hour) at pH 5·5 and pH 6·8. It showed the same rates of decomposition as the acid—probably by reason of prior hydrolysis—at pH 10·6 and in 1·0M-sodium hydroxide. In a borate buffer (1·5M-H_3BO_3; 1·5M-NaOH), at pH 8·7, the acid was stable, whilst the ester showed 30—35% apparent decomposition in 1 hour, but (presumably on account of hydrolysis) only 40—45% apparent decomposition in 2 hours. The rate of decomposition of the ester appeared to depend on the concentration of the phosphate buffers: later work on diphenyl-

methylnitramine has shown that this may have been caused by changes in [Na] rather than by changes in [PO_4].

Decomposition of p-*Nitrobenzylnitramine.*—The nitramine (0·2 g.) was warmed on a water-bath for 15 minutes with 0·2M-aqueous sodium hydroxide (10 ml.). After cooling, collection of the precipitate yielded 4 : 4′-diformylazoxybenzene (80 mg.) of m. p. 187°, undepressed by mixture with an authentic sample (Kirpal, *Ber.*, 1897, **30**, 1598). Crystallisation from acetic acid–water gave pure material, m. p. 191° (Found: C, 66·5; H, 4·2; N, 10·8. Calc. for $C_{14}H_{10}O_3N_2$: C, 66·1; H, 3·9; N, 11·0%). On decomposition in a closed system, M/20-solutions of the sodium salt in M/20- and M/1-sodium hydroxide yielded, respectively, 0·9 and 0·5 molecular proportion of gas; in the second case no azoxy-compound was precipitated. The gas evolved, in the absence of air, from a M/60-solution of the sodium salt in M/60-sodium hydroxide was found, on sampling, to be soluble in cold water (N_2O content, probably >90%).

Measurement of Decomposition Rates.—The nitramine (1 mg.-mol.) was placed in a suitable container, and brought into solution in 20 ml. of solvent (*e.g.*, for decomposition of a M/20-solution of the potassium salt of diphenylmethylnitramine in 1·0M-KOH + 1·0M-KCl, the solvent was 10 ml. of 2·05M-KOH and 10 ml. of 2·0M-KCl). The container was attached to the long (20 cm.) arm of a glass T-piece of *ca.* 7-mm. bore: this arm was cooled, between the container and the actual T-junction, by a 10-cm. condenser jacket. The arm leading off at right-angles was connected, through pressure tubing, to a gas-burette charged with mercury; and the third arm was drawn out to a capillary. The tightness of the apparatus was first tested by sealing the capillary and maintaining, for 30 minutes, a 15—20-cm. "head" of mercury. If gas-tight, the mercury was re-levelled, and the capillary broken: the container was then swung round and lowered, to a standard depth, into the thermostat. Tests showed that temperature equilibrium was reached in 5 minutes, at which time the capillary was re-sealed, and readings (of gas volume, at atmospheric pressure) commenced. The rate of warming suggested that the reaction time should be measured from 4 minutes after insertion into the thermostat, and the volume readings were extrapolated back to give a true initial volume, unaffected by thermal expansion. The readings were corrected to compensate for changes of pressure of the total volume enclosed, and for changes of temperature of the volume exposed beyond the condenser; the gas was assumed to be saturated with water vapour at the temperature of the cooling water passing through the condenser.

In the earlier experiments (runs I—XII) the container (a glass bulb of *ca.* 30-ml. volume) was sealed to the condenser. This was satisfactory for the more rapid decompositions (half-life 1—4 hours) but was not suitable for the slower reactions. The attack of the alkali on the glass produced, after about 12 hours, small but definite changes in the rate of reaction; and no account has been taken of any result obtained in glass after more than 8 hours' heating. It was, furthermore, impossible to estimate the residual nitramine (by acidification, ether-extraction, and titration) when a glass container had been employed. This was probably because of the presence, in the ethereal extract, of boric acid derived from the glass. In later work silver test-tubes (*ca.* 120 × 18 mm.) were employed. These were attached to the condenser by a rubber bung, and the joint made gas-tight by a film of cellulose acetate. This simple apparatus functioned satisfactorily, and appeared preferable to the more complicated use of a gasket. Apparent decomposition rates after prolonged heating in glass could be reproduced in silver by the initial addition of a few fragments of glass tubing to the solution: no such misleading values are quoted in this paper.

Determination of Residual Nitramine by Titration.—The solutions (in 1·0 M-potassium hydroxide) were cooled rapidly, acidified with aqueous sodium hydrogen sulphate (12·5 ml. of 2·1M.), and submitted

TABLE III.

Percentage of residual R·NH·NO_2.

R =	CH_3.	Ph_2CH.	$(p\text{-}C_6H_4Me)_2CH$.	$(p\text{-}C_6H_4Br)_2CH$.
By gas evolution	84	60, 44	57, 28, 28 *	39
By nitramine recovery	76	59, 46	57, 26, 29 *	35

* In 2·0M-KOH; acidified with adequate $NaHSO_4$.

to continuous ether-extraction. The extracts were dried (Na_2SO_4) (to remove any traces of aqueous bisulphate carried over), filtered, and evaporated through a fractionating column. The residues were dissolved in alcohol, and titrated, using phenolphthalein as indicator, with standard aqueous sodium hydroxide. The results are given in Table III; the low values for methylnitramine and for di-(*p*-bromophenyl)methylnitramine are not surprising, since methylnitramine is difficult to extract, and the comparatively rapid decomposition of the dibromo-compound probably brought about some loss in the period between the gas measurement and acidification.

Decomposition of 1-*Phenylethylnitramine and* 1-p-*Bromophenylethylnitramine in* 4 *and* 8M-*Potassium Hydroxide.*—Apparent first-order constants, 10^4k (min.$^{-1}$), in 4M-potassium hydroxide at 95°, and at, respectively, 90, 65, and 40% residual nitramine were:

For Ph·CHMe·NH·NO_2	0·3	0·3	—
For *p*-C_6H_4Br·CHMe·NH·NO_2	0·9	1·5	1·5

Similarly, in 8M-potassium hydroxide at 95°:

For Ph·CHMe·NH·NO_2	2·4	3·5	3·5
For *p*-C_6H_4Br·CHMe·NH·NO_2	1·4	1·9	2·3

It will be noted that in 8M-alkali the unsubstituted compound decomposed the faster, but, in view of the considerable deviations from the first-order rate, it is doubtful if the results are truly comparable.

Decomposition of Di-(p-bromophenyl)methylnitramine.—The considerable increase in the apparent reaction rate during the progress of the decomposition did not appear to be a simple example of autocatalysis. Solutions initially M/20, M/40, and M/80 in nitramine concentration (in 1·0M-potassium hydroxide, at 85°, for convenience in measurement) gave decomposition curves of a similar type. The prior addition of 4 : 4′-dibromobenzophenone (1 mol. per mol. of nitramine) to M/40- and M/80-solutions apparently caused a slight increase in the initial rate of decomposition, but no acceleration was thereafter observed. Under these conditions—the presence of more than one molecular proportion of (presumably) insoluble solid ketone—the first order of gas evolution was of the first order with respect to the nitramine, and was approx. equal ($k = ca.\ 4 \times 10^{-4}$ min.$^{-1}$) to that shown by the nitramine alone at 60% residual concentration. The influence of the ketone may be physical (surface effect?) rather than chemical. It is doubtful whether the degree of reproducibility of these results warrants their consideration in more than this qualitative fashion, and we refrain at present from further comment.

Measurement of the Dissociation Constants of the Nitramines.—The nitramine (1 mg.-mol.) was dissolved in aqueous alcohol (75 ml. of 50·5% v/v; d_4^{25} 0·933) and titrated potentiometrically at 20° with aqueous 0·1M-sodium hydroxide, using a standard Marconi pH-meter. The dielectric constant of the solvent was taken as 55·88 (by extrapolation of Akerlöf's values, *J. Amer. Chem. Soc.*, 1932, **54**, 4152), leading to a value of 0·9717 for the constant of the Debye–Hückel equation. The apparent thermodynamic dissociation constants are given in Table IV. No correction has been made for the error introduced by the use of a standard meter and glass electrode in aqueous alcohol. This is a constant error in all the results, and is probably less than 0·1 unit of pH (Speakman, *J.*, 1943, 270; Dole, *J. Amer. Chem. Soc.*, 1932, **54**, 3095). The results are, apart from this constant error, probably accurate to within 0·05 units of pK; and, for comparison, the values determined for a number of carboxylic acids, in the same manner, are included in the table.

TABLE IV.

Thermodynamic dissociation constants of the nitramines, R·NH·NO_2, *and carboxylic acids,* R·CO_2H, *in 50% v/v aqueous alcohol.*

R.	pK for R·NH·NO_2.	pK for R·CO_2H.	ΔpK.	R.	pK for R·NH·NO_2.	pK for R·CO_2H.	ΔpK.
Me	7·08	5·75	1·33	*p*-C_6H_4Br·CHMe	7·01	—	—
Ph	5·96	5·55	0·41	Ph_2CH	6·53	5·50	1·03
Ph·CH_2	6·92	5·56	1·36	(*p*-C_6H_4Br)$_2$CH	5·95	—	—
p-NO_2·C_6H_4·CH_2	6·36	4·99	1·37	(*p*-C_6H_4Me)$_2$CH ...	6·79	—	—
Ph·CH·CH_3	7·24	—	—	(*p*-MeO·C_6H_4)$_2$CH	6·77	—	—

The values for nitraminoacetic acid and its ethyl ester were determined in water at 20°, as previously described (Lindley and Speakman, *J.*, 1949, 1657). The ester has pK = 5·3; and the acid pK_1 = 3·2, pK_2 = 6·9. Comparison with methylenedinitramine (pK_1 = 5·0, pK_2 = 6·6; Lindley and Speakman, *loc. cit.*) and with malonic acid (pK_1 = 2·83, pK_2 = 5·69; Gane and Ingold, *J.*, 1931, 2158) is of interest, and suggests that, for power of electron attraction, $CO_2H > NH{\cdot}NO_2 > CO_2Et > \overline{N{\cdot}NO_2} > CO_2^-$.

Isolation of the Products of Decomposition.—(a) *From diphenylmethylnitramines.* After gas evolution had ceased, the residual alkaline suspension was cooled, and extracted with methylene dichloride. On evaporation, the following ketones were obtained (yields in parenthesis): benzophenone (95%), 4 : 4′-dimethyl- (84%), 4 : 4′-dimethoxy- (88%), and 4 : 4′-dibromo-benzophenone (99%).

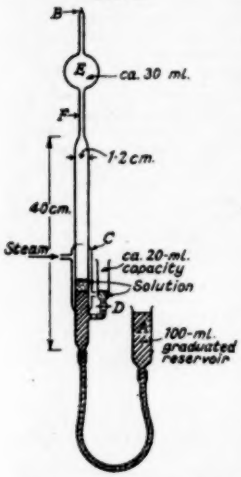
(b) *From benzylnitramine.* Extraction, as in (*a*), gave benzaldehyde (weighed as 2 : 4-dinitrophenylhydrazone) in 31% yield. Acidification of the aqueous layer, and re-extraction with ether, gave crude benzoic acid (identified by mixed m. p.) on evaporation. On the assumption that the acid was produced by the Cannizzaro reaction, the yield corresponded to a further 48% of benzaldehyde.

(c) *From 1-phenylethylnitramine and 1-p-bromophenylethylnitramine.* The strongly alkaline solutions (8M. and 4M., respectively) were cooled, diluted with water, and extracted with ether. The extracts yielded the 2 : 4-dinitrophenylhydrazones of acetophenone and of *p*-bromoacetophenone (identified by mixed m. p. with authentic specimens) on evaporation and treatment with 2 : 4-dinitrophenylhydrazine in methanol–sulphuric acid.

Stability of Phenylnitramine.—After 20 ml. of a N/20-solution of the potassium salt had been heated for 72 hours at 95° in 1·0M-potassium hydroxide, with no sign of gas evolution, the nitramine was freed by acidification with a slight excess of 2M-hydrochloric acid, and extracted with ether. The ethereal solution was dried, basified with *iso*propylamine, and evaporated to half its volume to remove excess of base. After cooling, the salt was collected; a further crop was obtained by evaporation to dryness, and trituration with ether. The identity of the salt (84% yield) was proved by its m. p. and mixed m. p. with authentic material. In a similar manner 85% and 74% yields of the *iso*propylamine salt were obtained after the nitramine had been heated at 95° for, respectively, 23 days in 4M- and 21 days in 8M-potassium hydroxide. During these runs a portion (*ca.* 2·2 and 5·0 ml., respectively) of the air enclosed in the apparatus was absorbed.

Collection and Analysis of the Gas obtained from Methylenedinitramine, and from Diphenylmethylnitramine.—The apparatus sketched in Fig. 2 was used. The reservoir *A* was raised, with the capillary *B* unsealed, to bring the mercury to the top of *B*. The capillary *B* was then sealed, and *A* lowered to bring the mercury surface within the jacket *C*. The aqueous solution of the nitramine was introduced cautiously through the tap *D*; as a quantitative measurement of the volume evolved was not required, a portion of the solution was left to act as a seal. Decomposition was brought about by passage of steam through *C*. When sufficient gas had been produced—as indicated by the position of *A* required to maintain the aqueous solution within the jacket *C*—the heating was stopped, and the capillary *B* briefly flamed to remove condensate. After a few minutes' drainage, the bulb *E* was sealed at *F* whilst the aqueous solution was still warm (*ca.* 70°). Analyses gave the following results: Sample from diphenylmethylnitramine in 2·5M-potassium hydroxide; water, 15 mg.; nitrogen, 15·5 mg. (100% by vol.): nitrous oxide and oxygen, 0. Sample from methylenedinitramine in 1·5M-potassium hydroxide; water, 13 mg.; nitrogen, 10·8 mg. (54% by vol.); nitrous oxide, 14·2 mg. (45% by vol.); oxygen, 0·1 mg. (1% by vol.). The small apparent percentage of oxygen, obtained by difference of two volumes each measured to 0·05 ml. (≏0·05 mg. of oxygen) is of doubtful significance. No hydrogen, carbon monoxide, nitric oxide, or hydrocarbon was detected in either case.

FIG. 2.



Preparation of Materials.—Nitraminoacetic acid and its ethyl ester were prepared according to Hantzsch and Metcalf (*loc. cit.*); *p*-nitrobenzylnitramine according to Hantzsch (*Ber.*, 1898, **31**, 180); and three of the diphenylmethylnitramines according to Gillibrand and Lamberton (*J.*, 1949, 1883).

Di-p-*methoxyphenylmethylnitramine.* 4 : 4′-Dimethoxybenzophenone hydrazone (5·2 g.) (Staudinger and Kupfer, *Ber.*, 1911, **44**, 2210) was shaken for 15 minutes, in an atmosphere of nitrogen, with yellow mercuric oxide (4·8 g.) suspended in ligroin (60 ml.; b. p. 40—60°). Alcoholic potassium hydroxide (2 ml. of 1·5M.) was used as a catalyst. The diazo-compound was dissolved by warming it with additional ligroin (100 ml.), and freed from inorganic material by filtration. On cooling in ice diazodi-*p*-methoxyphenylmethane (3·1 g.; m. p. 99—101°) separated; Staudinger and Kupfer (*loc. cit.*) give m. p. 103—104°. Nitrourethane (1·6 g. in 10 ml. of ether) was added to a solution of the diazo-compound (3·1 g. in 50 ml. of benzene). After effervescence slackened (30 minutes), the reaction was completed at 40°. The mixture was then cooled, and set aside overnight after the addition of *iso*propylamine (2·5 ml.). The *iso*propylamine salt (3·8 g.) was collected, dissolved in water, and acidified with dilute hydrochloric acid. The crude nitramine was then extracted with ether, and purified by precipitation as the ammonium salt, which was collected (2·9 g.), dissolved in cold water (50 ml. at 0°), and acidified with potassium dihydrogen phosphate (24 ml. of 1·0M). The oily precipitate, which slowly solidified, was collected: the *nitramine* (1·9 g.) was obtained as fine prisms, m. p. 68°, when a solution in *cyclo*hexane (*ca.* 30 ml.) and sufficiency of ether was allowed to evaporate slowly (Found: C, 62·8; H, 5·6; N, 9·4%; equiv., 284. $C_{15}H_{16}O_4N_2$ requires C, 62·5; H, 5·6; N, 9·7%; equiv., 288).

1-*Phenylethylnitramine.* Acetophenone azine (9·75 g.) (Scholtze and Locht, *J. Amer. Chem. Soc.*, 1926, **48**, 1032) was refluxed with anhydrous hydrazine (5 g.) (Smith and Howard, *Org. Synth.*, **24**, 53) for 30 hours (oil-bath at 130°). Most of the excess of hydrazine was then removed by azeotropic distillation with ligroin (b. p. 90—120°) under reduced pressure. When the overall weight was reduced to that required for the conversion into hydrazone, more ligroin (75 ml.; b. p. 40—60°) was added, and the last traces of hydrazine were destroyed by the addition of mercuric oxide until the colour of the latter persisted. Additional mercuric oxide (17·9 g.) was then added, together with alcoholic potassium hydroxide (0·5 ml. of 1·5M.), and the whole shaken for 1 hour. Filtration yielded a solution (estimated to contain 4·85 g. of diazomethylphenylmethane by Gillibrand and Lamberton's method, *loc. cit.*) to which nitrourethane (4·95 g. dissolved in the minimum volume of ether) was added cautiously. When the reaction had subsided, the resultant nitramide was decomposed by the passage of gaseous ammonia. The ammonium salt of the nitramine was collected, dissolved in water, and acidified with dilute hydrochloric acid. The precipitated *nitramine* was collected and crystallised from *cyclo*hexane to yield irregular plates (2·45 g.; 18% calc. on acetophenone azine), m. p. 92° (Found: C, 57·8; H, 6·1%; equiv., 166. $C_8H_{10}O_2N_2$ requires C, 57·8; H, 6·0%; equiv., 166).

p-*Bromoacetophenone azine.* The azine, prepared by Scholtze and Locht's general method (*loc. cit.*), crystallised from methylated spirits in plates (85% yield), and from *cyclo*hexane in needles. Both forms had m. p. 164° (Found: C, 49·4; H, 3·8; N, 7·1. $C_{16}H_{14}N_2Br$ requires C, 48·8; H, 3·6; N, 7·1%). The lack of colour is noteworthy; though the solutions were yellow, the solid had only an extremely faint tinge. An attempt to prepare the hydrazone by Barber and Slack's method (*J.*, 1944, 613) gave material of m. p. 140—150°, crystallisable to yield the azine. It appears that the m. p. (164°) given by these authors is that of the azine, not of the hydrazone.

1-p-*Bromophenylethylnitramine.* *p*-Bromoacetophenone azine (10 g.) and anhydrous hydrazine (2·45 g.), heated as described above, gave on addition of ligroin (b. p. 90—120°) a solid (10·4 g., presumably crude hydrazone) of m. p. 73°. This was suspended in ligroin (100 ml.; b. p. 40—60°) and, after addition of mercuric oxide (10·65 g.) and alcoholic potassium hydroxide (0·5 ml. of 1·5M.), the mixture was shaken, with wet-cloth cooling, for 90 minutes. The solution of diazomethyl-*p*-bromophenylmethane obtained by filtration (estimated content, 5·3 g.) was treated with nitrourethane (3·4 g.) in ether, and the mixture set aside overnight after the addition of *iso*propylamine (2·5 ml.). After

collection, the *iso*propylamine salt was dissolved in water, and the *nitramine* precipitated with dilute hydrochloric acid. Crystallisation from *cyclo*hexane yielded fine needles (2·9 g.; 26% calc. on the azine), m. p. 86° (Found: C, 39·3; H, 3·8; N, 11·8%; equiv., 243. $C_3H_6O_2N_2Br$ requires C, 39·2; H, 3·7; N, 11·4%; equiv., 245).

iso*Propylamine salt of phenylnitramine.* Phenylnitramine may be conveniently purified (and stored, if shielded from light) by conversion into the iso*propylamine* salt. The salt, precipitated from a dry ethereal solution of the nitramine by the addition of *iso*propylamine in ether, formed felted needles, m. p. 146° (decomp.) (Found: N, 21·6. $C_9H_{13}O_2N_3$ requires N, 21·3%).

We thank Dr. L. Phillips for the gas analyses, and Dr. J. C. Speakman for the potentiometric titration of nitraminoacetic acid and its ethyl ester.

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286. *The Liquid Dinitrogen Tetroxide Solvent System. Part III. The Electrical Conductivity of Liquid Dinitrogen Tetroxide.*

By C. C. ADDISON, J. ALLEN, H. C. BOLTON, and J. LEWIS.

The specific conductivity of liquid dinitrogen tetroxide has been found to be $1·3 \times 10^{-12}$ ohm^{-1} cm.$^{-1}$ at 17°. A conductivity cell and electrical circuit suitable for measurements of high resistances are described and the experimental features which may give rise to erroneously high conductivity values are discussed. The sign, and an approximate value for the temperature coefficient of conductivity have been determined and the possible mechanisms of electrical conduction in liquid dinitrogen tetroxide are considered.

A KNOWLEDGE of the electrical conductivity of liquid dinitrogen tetroxide was required for the interpretation of electrical measurements on solutions of various compounds in this liquid. Faraday (*Phil. Trans.*, 1840, **130**, 61) observed that the liquid distillate obtained by heating lead nitrate was a poor conductor of electricity; Frankland and Farmer (*J.*, 1901, **79**, 1356), finding the specific conductivity to be less than 2×10^{-6} ohm^{-1} cm.$^{-1}$, considered that the liquid was unable to behave as an ionising medium. Heberlein (see Mellor, "A Comprehensive Treatise, etc.," Vol. 8, p. 536) obtained values of $1·16 \times 10^{-6}$ to $14·2 \times 10^{-6}$ ohm^{-1} cm.$^{-1}$ over a temperature range of −10° to +20°.

A number of reactions in liquid dinitrogen tetroxide, involving nitrosyl compounds and nitrates, may be interpreted as "acid–base" reactions (Part I, *J.*, 1949, S 211, and following papers) on the basis of the dissociation $N_2O_4 \rightleftharpoons NO^+ + NO_3^-$ in the liquid state. In considering such reactions, it is not essential that this ionisation should occur to any appreciable extent in the pure liquid, but rather that the N_2O_4 molecule should serve as a potential source of these ions. In this respect the system is analogous to that of liquid ammonia, in which the ionisation $2NH_3 \rightleftharpoons NH_4^+ + NH_2^-$ is fundamental, although the specific conductivity of 10^{-11} ohm^{-1} cm.$^{-1}$ (Carvallo, *Ann. Physik*, 1914, **208**, 224) indicates that the degree of ionisation in pure liquid ammonia is very slight. Nevertheless, in a study of the nature of reactions involving liquid dinitrogen tetroxide it is of importance to determine whether such dissociation occurs to any appreciable extent in the pure liquid. To this end, various physical properties of the pure liquid have been studied. The present paper is restricted to conductivity studies; preliminary experiments indicated that the specific conductivity of the pure liquid was considerably smaller than previously recorded values, and since the electrical conductivity gives some indication of the presence of ionic species, its value has been determined accurately.

EXPERIMENTAL.

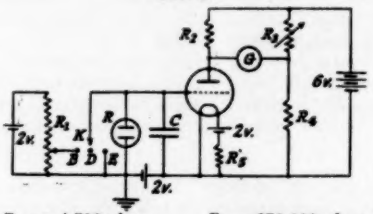
Preparation of Liquid Dinitrogen Tetroxide.—The liquid was prepared from lead nitrate (see Part II, *J.*, 1949, S 218). Dry powdered lead nitrate was heated in a steel tube; the evolved gases were passed down a water-cooled condenser fitted with a trap at the bottom. About one quarter of the dinitrogen tetroxide condensed here, together with any traces of metallic, and some of the aqueous, impurities. The remaining gas was then passed through a 40 × 2 cm. Pyrex glass tube packed with fresh phosphoric oxide, and was liquefied in a condenser [similar to that shown in Fig. 1 (*a*), Part II (*loc. cit.*), but without a thermometer] cooled to −15° in an ice–salt mixture. Before use, the condenser was washed in turn

with water, alcohol, and ether, warmed to 100°, and the ether vapour removed by blowing through dry nitrogen. Finally, the condenser was heated in a flame, cooled in a vacuum desiccator, attached to the tetroxide generator by a ground-glass joint, and guarded by a phosphoric oxide tube as described in Part II (*loc. cit.*). An empty bath was then placed round the condenser, and with this at room temperature, dinitrogen tetroxide gas was allowed to flow through until the apparatus was flushed free from air. Freezing mixture was then added slowly to the bath, and the temperature of the condenser decreased at such a rate that a steady out-flow of gas was maintained from the condenser. If the condenser was cooled rapidly, the fall in pressure due to the condensation of the tetroxide led to a rapid ingress of air and the consequent risk of entry of water vapour. Throughout the whole preparation the outflow of tetroxide from the condenser was maintained. Under these conditions the end of the phosphoric oxide guard tube became moist with nitric acid. To avoid the possibility of nitric acid flowing back into the condenser, the guard tube was bent downwards.

In order to ensure complete drying of the dinitrogen tetroxide in its passage through the phosphoric oxide column (immediately before the condenser) the gas was generated slowly, and liquefied in the condenser at the rate of about 5 ml. per hour. The liquid was redistilled (when required) directly from the condenser through phosphoric oxide columns of effective length 100 cm. and recondensed in a similar receiver with the same precautions as outlined above. To reduce the resistance to gas flow, the columns contained alternate bands of phosphoric oxide (3 cm.) and glass wool (1 cm.).

The product could be solidified at −11·2° to a colourless solid. [*Note.* The freezing point of liquid dinitrogen tetroxide was wrongly recorded in Part II as −9·3°. This should have read −11·2°, and the value recorded on the pure tetroxide axis in the NOCl–N_2O_4 phase diagram should be adjusted accordingly. All other points in this diagram are correct as recorded.]

FIG. 1.



R_2 = 4,700 *ohms.* R_4 = 270,000 *ohms.*
R_3 = 70,000 ,, R_5 = 10 ,,

Measurements of Electrical Resistance.—Preliminary experiments had shown liquid dinitrogen tetroxide to have a low electrical conductivity. It was therefore necessary to employ a method capable of measuring very high resistances. The method used involved measurement of the rate of decay of potential difference across a standard condenser, when the plates were connected through the high resistance. In this case, the high resistance consisted of a conductivity cell (described below) containing the liquid dinitrogen tetroxide. The voltage on the condenser must be measured by some instrument having a resistance considerably greater than the conductivity cell; for this purpose a G.E.C. electrometer valve, type E.T.I., was used. In this valve a high input resistance is achieved by having the grid connection isolated from other electrodes by a long glass neck. At the bias voltage (2 volts negative), the valve characteristics were such that the grid current was less than 10^{-16} amp. The electrical circuit employed is shown in Fig. 1; R represents the conductivity cell, and R_1 was a simple potentiometer device used to charge the mica condenser C, of capacity 0·01 μF. The Tinsley galvanometer G had a sensitivity of 16 cm. per microamp. at a mirror-scale distance of 1 m. The insulating parts of the simple three-way switch K were made from polystyrene. Other resistances were as stated. All accumulators used were of large capacity.

The circuit was shielded electrically by mounting the valve, switch, condenser, and resistances (other than R and R_1) in an earthed metal box. In order to prevent the formation of a film of moisture on the glass surface of the valve, and the consequent decrease in valve resistance, a tray of phosphoric oxide was placed inside the metal box some hours before a determination was carried out. The leads to the conductivity cell R were of stout (16 S.W.G.) uncovered copper wire, which passed unsupported through, and without touching, the shielding box.

The calculation of the value of R is based on the usual equation for rate of decay of voltage V across a condenser capacity C. At a given time t, $V_t = V_0 e^{-t/CR}$. The voltage concerned is the extra grid voltage applied from the potentiometer. In the initial calibration, it was necessary to confirm that the galvanometer deflection θ was proportional to V. In order to do this, switch K was set to point E, and R_3 adjusted to bring the galvanometer spot to the point of zero deflection on the scale. The switch was moved from E to B, thus applying an extra voltage (of the order of 0·5 volt or less) to the grid, and the resulting deflection measured. This was repeated for various settings of R_1, and it was confirmed that the deflection was proportional to this extra voltage. The above equation can therefore be written as $\theta_t = \theta_0 e^{-t/CR}$, whence $R = t/2{\cdot}303C.\ \log_{10}(\theta_0/\theta_t)$.

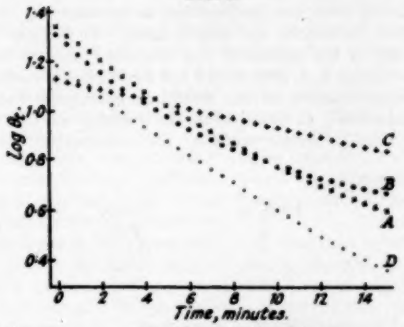
In a determination of R, the switch K was put to E, and the galvanometer set to zero deflection. The switch was then moved to B to charge the condenser C. The potentiometer was then isolated from C by switching from B to D, and the condenser voltage allowed to decay by discharge through R.

A graph of log θ against t was plotted as in Fig. 2, and the slope of the straight line used to calculate R. The capacity of the condenser was measured on a Marconi impedance bridge, and was found to be 0·0100 μF. ± 1%.

Conductivity Cell.—The cell used is shown in Fig. 3. In several standard types the leads are held rigid, and insulated from one another, by various forms of wax. Preliminary experiments showed that the bulk (or surface) conductivity of such waxes was frequently greater than that of the dinitrogen tetroxide itself. Under these conditions an accurate determination of the conductivity of the tetroxide was impossible. In the cell used, the leads to the electrodes were of 24 S.W.G., uncovered platinum wire, and were sealed directly through the glass walls of the cell; thereafter, the leads were separated by several cm. of air space. The electrodes, prepared from sheet platinum, had dimensions 3 × 1·3 cm., and were placed approximately 1 cm. apart. The cell constant, determined by using aqueous potassium chloride solution, was 3·81. The electrodes were contained in a glass tube about 6 cm. long and 3 cm. in diameter. This was sealed to a narrower tube 18 cm. long, carrying a B14 ground-glass joint C as shown.

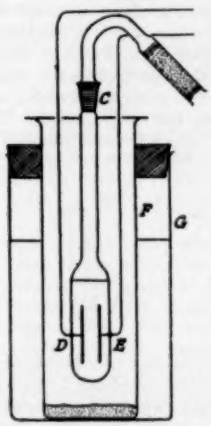
Before being filled with liquid tetroxide, the inside of the cell was scrupulously dried. This was done by washing with water, alcohol, and ether in turn; the cell was warmed to about 60°, and ether vapour removed in a stream of dry nitrogen. A narrow tube containing phosphoric oxide, sufficiently long to pass between the electrodes, and perforated at intervals, was then inserted into the cell. This drying tube was attached to a B14 ground-glass cone; the cell, thus sealed, was then allowed to stand for some days to remove traces of water from the inside walls. At the same time as the drying tube was removed from the cell, the guard tube protecting the condenser was removed, and the cone connected directly

FIG. 2.



Curve.	*Condition of cell surface.*
A	*Cell exposed to atmosphere.*
B	*Cell in P_2O_5 drying chamber for* 1 *hour.*
C	*Clean, dry surface* (10 *hours' drying*). *Adsorbed film of nitric acid.*

FIG. 3.



to C. Enough liquid was then poured over to cover the electrodes (about 35 ml.), and the cell protected by a guard tube as shown.

Surface Conduction.—The major error in determination of the resistance between the electrodes arises from surface conduction through films of moisture or acid absorbed on the outer surface of the glass cell between the sealing points D and E. If no attempt was made to dry the air immediately surrounding the cell, this surface conduction resulted in a log θ–t curve of type A (Fig. 2). Change in the slope of this curve indicates that the measured resistance, and thus the conductivity of the film, varies with time, and under no such conditions was a linear relation between log θ and t obtainable. The cell was therefore housed in a tall glass jacket F (Fig. 3) having a layer of phosphoric oxide at the bottom, and closed at the top by a cardboard lid. The leads from the cell passed, without contact, through two holes in this lid. The function of the long glass neck on the cell was to remove that part of the cell between D and E as far as possible from any water vapour which may diffuse through the holes in the lid. As the film of moisture was removed, the resistance increased. Curve B (Fig. 2) was obtained one hour after the cell was placed in jacket F. The rate of change of slope of curve B is greater than for curve A, indicating that the film is being removed; the overall slope, determined from the first and last experimental points, is less in B than in A, indicating an increase in resistance. After 10 hours' drying in F, the curve changed to the straight line C, and from this slope the true resistance was calculated.

In order to obtain true linear decay as shown by C, it was necessary to wash with water, and dry the outside of the cell immediately before placing it in jacket F (*i.e.*, after filling with tetroxide). If this precaution was not observed, and if the cell was allowed to come into contact with dinitrogen tetroxide vapour before being placed in the jacket, the slope of the log θ–t curve was observed to diminish on drying the cell, but the curvature could never be completely eliminated. Curve D (Fig. 2) is typical of the final results obtained under these conditions. This effect is attributed to the formation between

D and *E* on the cell surface, of a film of nitric acid produced by hydrolysis of the tetroxide. Unless this film was washed away by water, it could not be removed after placing the cell in *F*. The greater overall slope of curve *D* than of curves *A*, *B*, and *C* is consistent with the higher conductivity which a film of nitric acid might be expected to show, compared with a corresponding water film.

The resistance of the empty cell and associated circuit was also determined. This was found to be $1{\cdot}3 \times 10^{13}$ ohms. This high value confirmed that the drying procedure for both cell and electrometer valve was sufficient to reduce surface conduction to negligible proportions; it was possible to neglect the resistance of the cell and circuit in calculating the resistance of the liquid dinitrogen tetroxide.

Variation in Temperature.—For the measurement of resistance below room temperature, jacket *F* was surrounded by a further vessel *G*. With the cell in position, and the surrounding atmosphere in *F* dry, crushed ice was added to vessel *G*, which was then stoppered. By this means the temperature in the cell was decreased slowly. For a given quantity of added ice, preliminary experiments showed that the cell reached a steady temperature after about one hour. A resistance measurement, requiring about 15 minutes, could then be carried out with little change in temperature. For these measurements, the guard tube was replaced by a thermometer having a ground-glass cone fitting into socket *C* (Fig. 3), and of such a length that the bulb was immersed in the cell liquid. In order to measure resistances below 0°, it would be necessary to modify the apparatus to ensure more rigorous exclusion of moisture from the neighbourhood of the cell. However, the arrangement shown in Fig. 3 was found to be quite efficient over the temperature range for which results are recorded below.

Results and Discussion.

The results, given in Table I (where the specific conductivity κ is in ohm^{-1} $cm.^{-1}$), indicate that there is a slight variation in conductivity from one preparation to another; in view of the extremely low order of conductivity, such variations are unavoidable. It is clear that the drying system employed in the preparation of the tetroxide was efficient, since further redistillation through phosphoric oxide (Preparations 1, 4, and 5) did not decrease the conductivity. In fact, the reverse occurred, repeated redistillation of the tetroxide increasing rather than decreasing the conductivity. This is considered to arise from the passage of the tetroxide through an additional number of glass vessels before reaching the conductivity cell. The

Table I.

Prep. no.	Temp.	$10^{12}\kappa$.	Prep. no.	Temp.	$10^{12}\kappa$.
1 *	19·5°	2·61	6	20·4°	2·24
2	18·3	2·71	7	17·3	1·34
3	18·5	7·05		17·0	1·24
4 *	18·0	8·08	8	20·0	1·92
5 *	20·0	5·90		20·0	2·00

* N_2O_4 redistilled.

second of the two results recorded in each case for preparations 7 and 8 are duplicate measurements carried out about 7 hours after the first measurements, and indicate that the conductivity was constant within experimental error. These two experiments are considered to be the most accurate. Since any unconscious relaxation of the experimental precautions can only increase the conductivity, we consider Experiment 7 to approach most nearly to ideal conditions, and throughout later work we quote the electrical conductivity of liquid dinitrogen tetroxide as $1{\cdot}3 \times 10^{-12}$ ohm^{-1} $cm.^{-1}$ at 17°. This conductivity is the value obtainable from dinitrogen tetroxide prepared and purified as described above; it is possible that purification of the liquid to a higher degree than was required in this work may result in an even lower value for the conductivity than that quoted above.

The direction, and order of magnitude, of the temperature coefficient of conductivity has also been determined. For this purpose Preparation 6 (Table I) was used, and the conductivity values over a range of temperature are recorded below. Over this narrow temperature range the conductivity increased almost linearly with temperature, with a coefficient of $8{\cdot}5 \times 10^{-14}$ ohm^{-1} cm^{-1}./degree.

Temperature	7·3°	13·6°	19·5°	20·4°
$10^{-12}\kappa$ (ohm^{-1} $cm.^{-1}$)	1·17	1·71	2·19	2·24

In Table II the conductivity value and the sign of the temperature coefficient are compared with the corresponding properties of liquids which have been established as solvent systems.

With liquid ammonia, as with liquid dinitrogen tetroxide, developments in the technique of drying the liquid and apparatus have led to progressive decreases in the values for conductivity quoted in the literature. The positive sign of the temperature coefficient is taken from the work of Frenzel (*Z. Electrochem.*, 1890, **6**, 477) and Goodwin and Thompson (*Physical Rev.*,

1899, **8**, 38) although the conductivity values recorded by these authors are of the order of 10^{-7} and 10^{-4} ohm^{-1} cm.$^{-1}$, respectively.

The extremely low order of electrical conduction found for liquid dinitrogen tetroxide is in accord with observations made on many other pure liquids. In water and liquid ammonia (which have dielectric constants which are high compared with that of dinitrogen tetroxide) any ions produced by dissociation may be considered to be free to migrate, but although these ions have a high mobility the electrical conductivity is slight. This has been interpreted

TABLE II.

	κ (ohm^{-1} cm.$^{-1}$).	Temp. coeff.		κ (ohm^{-1} cm.$^{-1}$).	Temp. coeff.
Liquid N_2O_4	$1{\cdot}3 \times 10^{-12}$ at 17°	Positive	Water	(*b*) 4×10^{-8} at 18°	Positive
Liquid NH_3	(*a*) 10^{-11} at −33·4°	Positive	BF_3	(*c*) $8{\cdot}0 \times 10^{-9}$ at 25°	Negative

(*a*) Carvallo (*loc. cit.*).
(*b*) Kohlrausch and Heydweiller (*Z. physikal. Chem.*, 1894, **14**, 317).
(*c*) Banks, Emeléus, and Woolf (*J.*, 1949, 2861).

(Sidgwick, *Ann. Reports*, 1934, **31**, 42) as arising from the association of the molecules in the liquid state, with the formation of zwitterions which cannot contribute to the conductivity. In liquid dinitrogen tetroxide the N–N bond is so weak that association between neighbouring molecules may well occur. This, together with the limited ionic freedom which results from the low dielectric constant, gives rise to conditions in the liquid which are even less favourable for the conduction of electricity than in the case of water and liquid ammonia.

The small degree of conduction which does occur in liquid dinitrogen tetroxide may arise from either ionic or electronic conduction. If conduction is ionic, the low conductivity value indicates that the number of free ions is extremely small, and this is consistent with the low value observed for the dielectric constant (Part IV, following paper). The most probable ionic species are NO^+, NO_3^-, NO_2^+, and NO_3^-; the general chemistry of each ionic species suggests that they are thermally stable over the temperature range involved, and therefore a positive temperature coefficient would be expected. The negative coefficient for bromine trifluoride is attributed by Banks, Emeléus, and Woolf (*loc. cit.*) to the thermal instability of the ions responsible for conduction.

The term electronic conductivity is used here in its widest sense, to imply the transference of electricity by electrons rather than by charged ions. This form of electrical conductivity is normally associated (*e.g.*, in metals) with a negative temperature coefficient and a high conductivity value, but the peculiar nature of the NO_2 group makes this form of conduction theoretically possible. This group is known to exist in the three forms NO_2^+, NO_2, and NO_2^-; the paramagnetism of the uncharged group shows the presence of an unpaired electron, and the stability of the NO_2^+ and NO_2^- ions indicates the ability of the NO_2 group to donate or accept electrons. It is therefore possible to consider the passage of an electric current through the liquid as occurring by the transfer of electrons along a type of Grotthuss chain of NO_2 groups. In the present experiments, the potential difference across the electrodes did not exceed 2 volts. If an electronic mechanism operates, a different value for the conductivity may be obtained if a high potential difference is applied across the electrodes; this aspect is being investigated. The N_2O_4 molecule is diamagnetic, and is less likely to partake in such a mechanism. The low order of conductivity may then be related to the small concentration of NO_2 groups in the liquid tetroxide. Soné (*Sci. Rep., Tohoku Imp. Univ.*, 1922, **11**, 139), from a study of magnetic susceptibility, has deduced that liquid dinitrogen tetroxide undergoes homolytic dissociation to the extent of 0·15% at 0° and 0·72% at 20°. If the conductivity is electronic, and is a property of the NO_2 groups, then the positive temperature coefficient which would arise from the increase in dissociation with temperature may outweigh the negative coefficient usually associated with electronic conduction in systems where no such dissociation can occur.

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287. *The Liquid Dinitrogen Tetroxide Solvent System. Part IV. The Dielectric Constant, Refractive Index, and Polarisation of Liquid Dinitrogen Tetroxide: the Nature of Solutions.*

By C. C. Addison, H. C. Bolton, and J. Lewis.

The dielectric constant of liquid dinitrogen tetroxide has been found to be 2·42 at 18°. Values of the refractive index are recorded for several wave-lengths. The molar polarisation, and molar refractivity, have values 26·5 c.c. and 15·2 c.c., respectively. Factors responsible for this difference are discussed, and the influence of low dielectric constant on the nature of solutions in liquid dinitrogen tetroxide is considered.

In a consideration of electrical phenomena and mode of chemical reaction in liquid dinitrogen tetroxide, a knowledge of the dielectric constant is fundamental. Schlundt (*J. Physical Chem.*, 1904, **8**, 122), using Drude's method (*Z. physikal. Chem.*, 1897, **23**, 267), obtained the values 2·56 (at 15°) and 2·6 (at −40°) for the dielectric constant of dinitrogen tetroxide. This value, of the same order as that of benzene, *viz.*, 2·284 (van der Maesen, *Physica*, 1949, **15**, 481), is very low in comparison with those of water (81·1) and liquid ammonia (17·8 at 15°). It is therefore to be expected, from the Nernst–Thomson rule, that salts dissolved in liquid dinitrogen tetroxide will not undergo appreciable dissociation into free ions. In accordance with this, it has been observed that solution of alkylammonium salts in dinitrogen tetroxide have a negligible electrical conductivity. However, the reactions of these salts in solution are ionic in character (Part I, *J.*, 1949, S 211), and certain compounds, when dissolved in the tetroxide, give conducting solutions. For these reasons, it was considered necessary to redetermine the dielectric constant of liquid dinitrogen tetroxide.

The refractive index of the liquid at infinite wave-length has also been determined in order to obtain information on the relative significance of the various forms of polarisation in the pure liquid.

Experimental.

Construction of Condenser.—The dielectric constant was determined by comparing the capacity of a specially prepared condenser in air and in liquid dinitrogen tetroxide. In view of the low order of the dielectric constant, it was necessary to increase, as far as was practicable, the area of the plates, and to decrease their distance apart. A pattern commonly used for such a purpose employs two concentric glass tubes having the annular surfaces silver-plated. The advantages of this pattern are, first, that a high capacity is obtained in a small volume, thus minimising the amount of liquid required, and secondly, that the space between the plates is shielded electrically from any stray fields. Silver could not be used in this determination, as it is attacked by the tetroxide. Pure nickel is not attacked, and the apparatus used is shown in the figure. The condenser *A* consisted of two concentric cylinders prepared from nickel sheet 1·5 mm. thick. The outer cylinder was 5 cm. long and had a diameter of 2 cm. The inner cylinder was of identical length, and of such a diameter as to give an annular gap of about 1 mm. By this means the stray capacity arising from the spreading of the lines of force from the ends of the condenser was reduced. The cylinders were held rigidly with respect to one another by spacers of thin glass rod pressed into the annulus. The leads *B* (which were continuous with the metal of the cylinders) were 2 × 1·5 mm. nickel strips and were soldered to stout (16 S.W.G.) uncovered copper wires *C*. The condenser was held rigid by embedding the leads *B* in a B 24 ground cone *D* filled with beeswax and picein, as illustrated in the figure.

Conditions of Measurements of Capacity.—The capacity, as measured, is the sum of the true capacity of the condenser and the stray capacity arising mainly from the leads. For accurate measurement of dielectric constant it was necessary (*a*) to manipulate the apparatus so that the stray capacity was kept constant throughout the whole series of measurements, and (*b*) to determine the magnitude of this stray capacity by the use of a standard liquid. Benzene was chosen for this purpose since it has a dielectric constant close to Schlundt's value for dinitrogen tetroxide (*loc. cit.*). Hence the determination of the dielectric constant involves the measurements of three capacities:

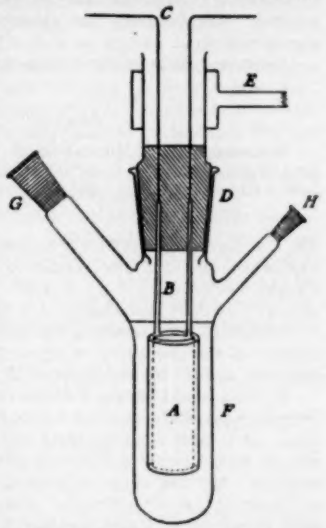
$$C_1 = C_s + C \text{ (in air)}$$
$$C_2 = C_s + \varepsilon_1 C \text{ (in benzene)}$$
$$C_3 = C_s + \varepsilon_2 C \text{ (in dinitrogen tetroxide)}$$

where C_s is the stray capacity, and C the capacity of the condenser in air. Hence the dielectric constant of dinitrogen tetroxide is given by:

$$\varepsilon_2 = 1 + (C_3 - C_1)(\varepsilon_1 - 1)/(C_2 - C_1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Manipulation of Apparatus.—The condenser was washed with water, alcohol, and ether, freed from solvent in a stream of warm, dry nitrogen, and allowed to cool in a vacuum desiccator. The cone *D* carrying the condenser was then fixed rigidly (clamp *E*), and the leads *C* to the electrical circuit were also fixed in position. Throughout each series of measurements the position of condenser and leads

remained unaltered, so that the stray capacity was constant. The vessel *F* was thoroughly dried by the technique described in the previous paper, phosphoric oxide guard tubes were attached at *G* and *H*, and *F* was placed in position as shown in the figure. The total capacity in air (C_1) was then determined. Without any alteration in the position of the apparatus, liquid dinitrogen tetroxide was poured slowly into *F via* the B 14 ground joint *G*, until the condenser was covered. The guard tube was replaced at *G*, and the total capacity C_2 measured. Vessel *F* was then lowered from the condenser, and the latter was immediately washed with water, followed by alcohol and ether, and dried in a stream of nitrogen. A second vessel identical with the first vessel *F* and previously dried, was placed around the condenser, and the capacity in air redetermined to confirm that the condition of the condenser was unchanged. Pure benzene was then added to *F via G* until the condenser was covered to exactly the same extent as in the experiment using dinitrogen tetroxide, and the total capacity was determined. For measurement of capacity at other than room temperature, vessel *F* was surrounded by a bath kept at the desired temperature.



Purification of Materials.—The dinitrogen tetroxide was prepared and purified by the method given in Part III (preceding paper). The benzene was purified by Richards and Shipley's method (*J. Amer. Chem. Soc.*, 1914, **36**, 1825). This has become accepted by many workers (*e.g.*, Hartshorn and Oliver, *Proc. Roy. Soc.*, 1929, *A*, **123**, 664) as suitable for the exhaustive purification of benzene for dielectric-constant measurement, and involves successive treatments with sulphuric acid, sodium hydroxide, distilled water, and mercury; the liquid was finally dried by calcium chloride and sodium wire.

Measurements of Capacity.—Preliminary determinations were carried out as follows: (*a*) The capacity of the condenser *A* (see figure) was measured directly, a Mullard capacity-measuring bridge Type G.M. 4140/1, and 1000 c./s. oscillator unit Type G.M. 4260 being used. The capacity bridge was calibrated by using a Marconi Circuit Magnification Meter Type T.F. 329 G., and also a Muirhead variable air-condenser Type A-430-BMS. This method indicated that the dielectric constant was small, of the order of 2·4. The final value was determined by the following variation of the usual substitution method, which is more accurate than method (*a*).

(*b*) A condenser *D* and a Sullivan variable air-condenser *E* were placed in series, and their total capacity was measured. The test condenser *A* was placed across *D* and *E*, and *E* adjusted until the balance was restored. If E_1 is the second value of the air condenser, then

$$C_A = C_D^2(C_E - C_{E_1})/(C_D + C_E)(C_D + C_{E_1}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The capacity of *D*, which was measured accurately, was only slightly greater than that of *A*; therefore, the value of $C_E - C_{E_1}$ was large, and in consequence the errors in reading the scale *E* were reduced.

Refractive Index.—This value was determined by the method of minimum deviation, a hollow 60° glass prism and a 6″ Precision Instrument Co. Spectrometer being used. Values were obtained at four different wave-lengths by means of mercury and sodium vapour lamps.

Results and Discussion.

By using equation (2) and method (*b*) above, the capacity of condenser *A* was determined with air, benzene, and liquid dinitrogen tetroxide (C_1, C_2, and C_3, respectively in equation 1) as dielectrics. The results are given in Table I. The series of results given for the capacity of condenser *A* were obtained for different settings of the variable condenser, and represent the order of reproducibility of the capacity measurements. All measurements recorded in Table I were carried out at 18°, and at a frequency of 1000 c./s. The error attached to the final value of ε cannot be greater than 1%.

Influence of Temperature on Dielectric Constant.—When the temperature of the liquid dinitrogen tetroxide was reduced from 18° to −5° by surrounding vessel *F* by a freezing mixture, there was an almost negligible change in the dielectric constant. Since the proportion of

Table I.

Dielectric:	Air.	Benzene.	Liquid N_2O_4.
Capacity A ($\mu\mu$F.)	58·8	123·2	130·1
	58·6	123·5	130·1
	58·0	123·5	130·4
	58·8	123·9	130·3
	—	123·6	130·8
Mean capacity ($\mu\mu$F.)	58·5	123·5	130·3
Dielectric constant ε	1	2·284 *	2·42 (calc. by eqn. 1)

* Van der Maesen (*loc. cit.*).

nitrogen dioxide in the liquid tetroxide varies appreciably over this temperature range, it may be of some significance that the dielectric constant is almost independent of temperature. The measurements obtained showed a slight increase in the value of the dielectric constant at lower temperatures, but since the change in capacity was little more than the experimental error of capacity measurement, no attempt has been made to assess the temperature coefficient quantitatively.

Refractive Index.—The values determined for a series of wave-lengths are given in Table II.

TABLE II.

Wave-length, Å.	Angle of * minimum deviation, D.	n (at 20°).	Wave-length, Å.	Angle of * minimum deviation, D.	n (at 20°).
5893 (Sodium)	30° 19·5′	1·420	4916·4 (Hg blue-green)	31° 11·7′	1·431
5460·7 (Hg green)	30° 38·5′	1·424	4358·3 (Hg blue)	32° 6·2′	1·442

* Angle of prism = 59° 47·9′.

The measured angle ($2D$) was reproducible within 1′, giving values of n which are correct to four significant figures. The refractive index at infinite wave-length (n_∞) was determined from Cauchy's relation $n_\lambda = n_\infty + a/\lambda^2$. Extrapolation of the straight line obtained by plotting n_λ against $1/\lambda^2$ gave the value $n_\infty = 1{\cdot}394$.

Significance of Results.—The results given above are of value in the study of two separate aspects of the chemistry of liquid dinitrogen tetroxide, *i.e.*, (*a*) the nature of solutions in this medium, and (*b*) the constitution of the pure liquid itself.

(*a*) In a liquid having a dielectric constant as low as 2·42, the coulombic forces of attraction between oppositely charged ions will be sufficiently large to prevent their separation into free ions. It is clear from the work of Fuoss and Kraus (*J. Amer. Chem. Soc.*, 1933, **55**, 476, *et seq.*) that in such a liquid a dissolved salt will exist almost entirely in the form of ion-pairs in dilute solution; increase in concentration may result in a more complex type of ion association, such as the formation of triple ions. This is considered to be the state of solutions of alkylammonium salts dissolved in liquid dinitrogen tetroxide. Ion-pairs do not contribute to the electrical conductivity of the solution, and in consequence the electrical conductivities of freshly prepared solutions of alkylammonium salts in dinitrogen tetroxide at concentrations as high as 30% are less than 10^{-8} ohm^{-1} cm.$^{-1}$. However, this concept is not necessarily in conflict with the apparently ionic nature of reactions in liquid dinitrogen tetroxide (Part I, *J.*, 1949, S 211; Part V, following paper); but such reactions must be considered as occurring as a result of collision between ion-pairs rather than free ions. In reactions between ions, or ion-pairs, the activation energy is influenced by the dielectric constant; but it is only the rate, and not the character, of the reaction which is so influenced (Moelwyn-Hughes, " Kinetics of Reactions in Solution," Oxford Univ. Press, 1947, p. 92). Certain compounds (*e.g.*, diethylnitrosamine) when added to liquid dinitrogen tetroxide give rise to strongly conducting solutions. In the interpretation of these high conductivities, the increase in dielectric constant of the medium arising from the addition of nitrosamine to dinitrogen tetroxide is no less important than the ionic character of the compound formed between these two components. This work is described in Part VI (*J.*, 1950, 1303).

(*b*) The data given above may be used to determine the difference between the molar polarisation (P) and the molar refraction ($[R]$) for pure liquid dinitrogen tetroxide. Using the expression

$$\text{Molar polarisation} = P = M(\varepsilon - 1)/\rho(\varepsilon + 2)$$

and accepting the value for the density (ρ) as 1·444 at 20° (Ramsay and Shields, *J.*, 1893, **63**, 1089), we find that $P = 26{\cdot}5$ c.c. Substituting the value of the refractive index at infinite wave-length (n_∞) into the expression

$$\text{Molar refraction} = [R] = M(n^2 - 1)/\rho(n^2 + 2)$$

we find $[R] = 15{\cdot}2$ c.c.

In the absence of permanent dipoles and infra-red polarisation effects, P will equal $[R]$. This state is approached in a number of non-polar liquids; *e.g.*, assuming the value $n_\infty = 1{\cdot}476$ for benzene (by extrapolation from Brühl's data, *Z. physikal. Chem.*, 1897, **22**, 373), we find $P = 34{\cdot}68$ c.c. and $[R] = 32{\cdot}92$ c.c. The divergence observed between P and $[R]$ for liquid dinitrogen tetroxide is therefore to be attributed to one or both of the above factors. Although the molar polarisation determined from the static dielectric constant ε is the sum of the electronic polarisation, the polarisation due to permanent dipoles, and atomic polarisation (*i.e.*, the polarisation arising from nuclear vibrations, due to absorption in the infra-red), the contribution

made by the latter factor is normally relatively so small in liquids having permanent dipole moments that it is often neglected. In purely non-polar liquids, where there is no variation in ε with temperature, any discrepancy between $[R]$ and P is associated with infra-red absorption, since, as the value of n used is that at infinite wave-length, $[R]$ is a true measure of the electronic polarisation. However, in liquid dinitrogen tetroxide the position is more complex, since it is not possible to deduce from the near-zero value of $d\varepsilon/dT$ that no dipolar components are present. This arises from the following considerations: (*a*) The dipole moment of the dinitrogen tetroxide molecule has been shown by Williams, Schwingel, and Winning (*J. Amer. Chem. Soc.*, **1936**, **58**, 197) to differ little, if at all, from zero, but the nitrogen dioxide molecule has a dipole moment (in the gaseous state) of 0·58 D. at 25°. (*b*) The concentration of nitrogen dioxide increases with temperature. (*c*) In a polar liquid, the total polarisation decreases with increasing temperature. Thus the temperature independence of dielectric constant of liquid dinitrogen tetroxide could be achieved by a balance between the factors (*b*) and (*c*).

It is not yet possible to assess the extent to which atomic polarisation is responsible for the difference between P and $[R]$, but this difference (11·3 c.c.) is significantly greater than that usually attributed to infra-red absorption effects. Unless this factor is completely responsible, it follows from the above that the discrepancy may be attributed to the presence of some polar component, in spite of the constancy of ε with temperature. In order to determine the extent to which the nitrogen dioxide molecules present in the liquid state could be responsible for this difference, the equation

$$\left[\left(\frac{\varepsilon-1}{\varepsilon+2}\right)-\left(\frac{n^2-1}{n^2+2}\right)\right]\frac{f_1M_1+f_2M_2}{\rho}=\frac{4\pi N}{3}f_2\left(\frac{\mu^2}{3kT}\right) \quad . \quad . \quad . \quad . \quad . \quad (3)$$

(see Debye, "Polar Molecules," Chemical Catalog Co., **1929**, p. 45) has been employed to calculate the contribution made by the nitrogen dioxide to the polarisation. If it is assumed (*a*) that Williams, Schwingel, and Winning's dipole moment values (*loc. cit.*) are not appreciably different from the values in the liquid state, and (*b*) that at 20° the liquid tetroxide contains 0·7% of nitrogen dioxide (Soné, *Sci. Rep. Tohoku Imp. Univ.*, **1922**, **11**, 139), the nitrogen dioxide makes a negligible contribution ($<0{\cdot}04$ c.c.) to the P–$[R]$ difference.

If we continue the assumption that atomic polarisation may be responsible for only part of the P–$[R]$ difference, it becomes necessary to seek an alternative dipolar component which could be present in the liquid state. There is considerable evidence, from its purely chemical reactions, that the dinitrogen tetroxide molecules in the liquid state react as nitrosyl nitrate. Angus, Jones, and Phillips (*Nature*, **1949**, **164**, 433) have represented the molecule in the convenient form $NO^{\delta+}-NO_3^{\delta-}$. In the limit, this may be represented by an ion-pair $[NO^+][NO_3^-]$. These forms of the molecule would possess dipolar character, and an equilibrium

$$N_2O_4 \rightleftharpoons NO^{\delta+}\text{–}NO_3^{\delta-} \rightleftharpoons [NO^+][NO_3^-]$$

could account for all or part of the difference between P and $[R]$. This equilibrium is postulated for the liquid phase; only one form of the molecule will occur in the solid, and polar forms of the molecules are unlikely in the gaseous state, so that this equilibrium is not in conflict with (*a*) crystallographic evidence for the structure of the molecule (Broadley and Robertson, *Nature*, **1949**, **164**, 915), (*b*) the absence of a dipole moment for the dinitrogen tetroxide molecule in the gaseous state, or (*c*) the low electrical conductivity of the liquid (Part III, preceding paper).

If $[NO^+][NO_3^-]$ is the polar constituent, then in equation (3), $M_1 = M_2$, and it follows that at any given temperature $f_2\mu_2^2$ has a constant value. If we assume an arbitrary value of 3 A. for the inter-ion distance in the ion pair, and that the whole $P - [R]$ difference arises from the presence of this component, then it may be calculated from the above relationship that the mol.-fraction f_2 of ion pairs in the liquid is as low as 0·001.

It is relevant that Goulden (Ph.D. Thesis, Univ. of London, **1949**) has observed that the Raman spectrum of liquid dinitrogen tetroxide at −10° (*i.e.*, immediately above its m. p.) shows no frequency in that region of the spectrum which is characteristic of the NO^+ ion. However, it has been stated above that if the difference between molar polarisation and refraction is to be attributed to the presence of a polar species, the concentration of that species should increase with temperature, so that a study of Raman spectra over a temperature range is necessary before the possibility of an equilibrium in the liquid state can be dismissed.

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288. *The Liquid Dinitrogen Tetroxide Solvent System. Part V. Reactions involving Some Alkylammonium Salts, with Particular Reference to Solvolysis and the Formation of Diethylnitrosamine.*

By C. C. Addison, C. P. Conduit, and R. Thompson.

Preliminary experiments with a number of alkyl-substituted ammonium chlorides have shown that these salts dissolve in, and react with, liquid dinitrogen tetroxide, to produce the corresponding nitrate and nitrosyl chloride. These reactions are considered from the point of view of solvolysis, and the reaction of diethylammonium chloride has been studied quantitatively. Variations with time in the physical properties of solutions of the nitrates of secondary amines in dinitrogen tetroxide indicate that a further reaction occurs between these components. The reaction between diethylammonium nitrate and dinitrogen tetroxide has been studied quantitatively; nitric acid and diethylnitrosamine are produced, and the possible significance of this nitrosamine as a true base in the dinitrogen tetroxide solvent system is discussed.

Solvolytic reactions in which a salt undergoes reaction with the medium in which it is dissolved to produce an acid and a base characteristic of that medium are well known in the aqueous system. Examples occur also in the bromine trifluoride system (Gutmann and Emeléus, *J.*, 1950, 1046), but solvolysis is much less clearly defined in liquid ammonia. On the basis of the dissociation $N_2O_4 \rightleftharpoons NO^+ + NO_3^-$ postulated in Part I (*J.*, 1949, S 211), the reactions of the alkylammonium chlorides with liquid dinitrogen tetroxide may be interpreted as solvolytic with respect to this medium. Neither ammonium chloride nor ammonium nitrate reacts with liquid dinitrogen tetroxide; pure diethylamine reacts explosively on contact with liquid dinitrogen tetroxide, but diethylammonium chloride reacts smoothly according to the equation

$$[Et_2NH_2]^+Cl^- + N_2O_4 \longrightarrow [Et_2NH_2]^+NO_3^- + NOCl \quad . \; . \; . \; . \; (1)$$

Under appropriate conditions the reaction proceeds smoothly in the direction shown; the nitrosyl chloride can be removed quantitatively under vacuum, and the diethylammonium nitrate crystallises in pure form on addition of ether.

This solvolytic reaction appears to be typical of the alkylammonium chlorides. A quantitative study of the reaction of the diethyl salt has been made; the following qualitative observations indicate the main features of the reactions between liquid dinitrogen tetroxide and some other alkylammonium salts.

Methylammonium Salts.—On the addition of crystals of the chloride to liquid dinitrogen tetroxide, a red coloration due to nitrosyl chloride developed immediately, and the liquid separated into two immiscible liquid phases. The upper phase contained a little nitrosyl chloride, but consisted mainly of methylammonium nitrate dissolved in dinitrogen tetroxide. The lower layer was a deep red solution of nitrosyl chloride in dinitrogen tetroxide, and contained only a trace of methylammonium nitrate. On warming the liquid or on applying vacuum, the nitrosyl chloride was readily removed, but the resulting liquid remained as two immiscible layers. It appears that the nitrosyl chloride has in itself little influence on the immiscibility, which arises from the presence of the amine salt. The formation of two immiscible layers is a general property of amine nitrates dissolved in liquid dinitrogen tetroxide; the range of concentration over which immiscibility extends depends upon the character and number of the substituent alkyl groups.

Dimethylammonium Salts.—The chloride dissolved readily in dinitrogen tetroxide; solvolysis occurred immediately on contact, but in this case no separation into two layers occurred. On long standing, or on rise of temperature, separation into two layers did occur; this is considered to arise from a slow reaction which follows the solvolytic reaction and introduces further components into the system. This aspect is considered in detail in connection with the diethyl compounds (p. 1300). Of the mono- and di-methylammonium salts, only the nitrates crystallised when the solution was concentrated by evaporation of the dinitrogen tetroxide.

Trimethylammonium Salts.—Solvolysis was again rapid with the chloride, and two liquid phases were produced. The nitrate appeared to be considerably less soluble than the

corresponding mono- and di-methyl compounds, since it crystallised spontaneously from the medium without preliminary concentration of the solution. The crystalline product consisted of pure trimethylammonium nitrate, m. p. 155°. When 0·5 g. of the pure nitrate was added to 9 ml. of dinitrogen tetroxide, dissolution of the salt was slow, requiring 1·5 hours' constant shaking. A similar quantity of dimethylammonium nitrate dissolved almost immediately.

Tetramethylammonium Salts.—The chloride dissolved rapidly; solvolysis produced a readily soluble nitrate and the liquid separated into two immiscible phases. It appears probable that in this case other reactions in addition to solvolysis occur. The red coloration due to nitrosyl chloride was much less pronounced, and while the solid was dissolving a transient green colour was produced, although precautions were taken to ensure that the added chloride was quite dry. On removal of the volatile constituents under vacuum, the crystalline nitrate obtained was entirely free from chloride. The two liquid phases formed on the addition of a small amount of the nitrate to a large excess of dinitrogen tetroxide persisted throughout the evaporation of the tetroxide, so that the two-liquid system appears to be typical of solutions of this nitrate over the full concentration range.

Ethylammonium Salts.—The reaction of the chloride followed closely that of the monomethyl salt. The nitrate was readily soluble, and could be separated from the upper layer by evaporation of the nitrosyl chloride and dinitrogen tetroxide.

Diethylammonium Salts.—The solvolytic reaction of the chloride has been given in equation (1), and is considered in detail below.

Triethylammonium Salts.—The solvolytic reaction followed the normal course, but in contrast to the trimethyl salt no separation into two liquid phases occurred. The triethylammonium nitrate is much more soluble in liquid dinitrogen tetroxide than is the trimethyl salt.

The reactions which the alkylammonium chlorides undergo in solution in liquid dinitrogen tetroxide are therefore analogous to their well-known hydrolysis in aqueous solution, and it is of interest that the solutions of the nitrates in liquid dinitrogen tetroxide possess miscibility gaps which resemble the well-known two-phase systems given by the alkyl-substituted ammonium hydroxides in water. In each medium the solvolytic reaction reaches a state of equilibrium, but in liquid dinitrogen tetroxide this equilibrium is displaced further towards complete solvolysis than in the corresponding aqueous solutions. Consistent with this is the fact that the hydrolysis of tetramethylammonium chloride is negligible in aqueous solution, though solvolysis proceeds to a marked degree in solution in liquid dinitrogen tetroxide.

The above observations are restricted to the chlorides. Similar initial reactions probably take place with the bromides and iodides also, but such reactions are complicated by the release of nitric oxide and free halogen. For example, nitrosyl iodide is not known to exist, and the addition of an alkylammonium iodide to liquid dinitrogen tetroxide results in separation of free iodine.

Although solvolysis appears to be a typical reaction of the alkylammonium chlorides, it is noteworthy that the general chemistry of liquid dinitrogen tetroxide includes very few other examples. The chlorides of silver, sodium, potassium, and many other metals are not attacked by liquid dinitrogen tetroxide, though it has been observed (by Mr. J. Lewis in this laboratory) that anhydrous zinc chloride reacts to give the nitrate and nitrosyl chloride. Partington and Whynes (*J.*, 1949, 3135) have observed that titanic chloride reacts to give some nitrosyl chloride, and although the nature of the metal salt produced is not certain, the reaction is no doubt solvolytic in character.

True solvolysis necessarily involves reactions which are of ionic nature. However, there are certain reactions involving non-ionic compounds which would appear, on a formal analogy, to be solvolytic in character; *e.g.*, methyl iodide is said to react according to the equation $2CH_3I + 2N_2O_4 = 2CH_3{\cdot}NO_3 + 2NO + I_2$ (Henry, *Bull. Acad. Belg.*, 1874, **38**, 7). Reactions carried out with methyl and ethyl iodides show that the iodine is produced slowly (over periods of minutes or hours depending on conditions); there seems to be no doubt that the mechanism of such reactions differs from the almost instantaneous ionic reactions involving the alkylammonium halides and reactions of this type are not considered to be solvolytic.

Stability of Solutions of Diethylammonium Nitrate.—In considering liquid dinitrogen tetroxide as a solvent system, we have assumed that the dissociation $N_2O_4 \rightleftharpoons NO^+ + NO_3^-$ is possible. It is known (Goulden and Millen, *J.*, 1950, 2620) that this heterolytic dissociation does in fact occur in solutions of dinitrogen tetroxide in nitric acid, and there appears to be no reason to doubt that it is possible in the pure liquid tetroxide. On this basis, the alkyl-substituted ammonium nitrates may be regarded as " bases " in this system (Cady and Elsey, *J. Chem. Educ.*, 1928, **5**, 1425). Solutions of these nitrates in liquid dinitrogen tetroxide have

been found to possess some of the properties typical of hydroxides in the aqueous system, *e.g.*, the rapid reaction with zinc metal to give soluble zinc complexes referred to in Part I (*loc. cit.*). During the course of the preliminary experiments on solvolytic behaviour described above, it was observed in some cases that slow reactions between the dissolved nitrate and liquid dinitrogen tetroxide followed the more rapid solvolytic reactions. This was pronounced in the case of the disubstituted salts, and since diethylammonium nitrate is amongst the most soluble, a qualitative and quantitative examination has been made of the nature of the reaction between this salt and liquid dinitrogen tetroxide in order to determine the stability of such " basic " solutions, and the significance of the reaction products in this solvent system.

Attempts were made to measure the freezing points, miscibility ranges, and electrical conductivity of solutions of diethylammonium nitrate in liquid dinitrogen tetroxide. In each case reaction between the two components gave rise to drifting values. Fig. 1 shows the variation in freezing point of a 62% w/w solution of the nitrate, and similar variations were found to occur at other concentrations. There is an approximately linear relationship between the freezing point and the logarithm of the age of the solution. At concentrations of the nitrate greater than 20% the solutions remained homogeneous even on long standing. In the 0—20% concentration range, the solutions were homogeneous immediately after preparation, but separated into two immiscible layers on standing for periods of time which depended on the concentration.

FIG. 1.

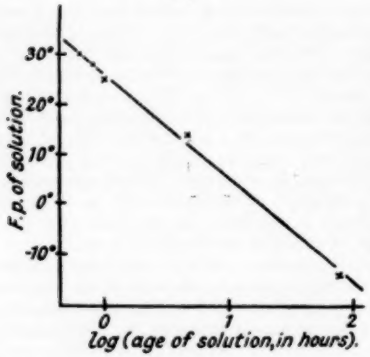
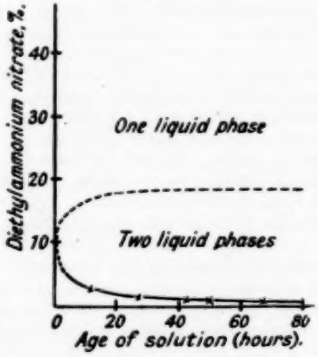


FIG. 2.



Within the 8—12% concentration range the two layers appeared within seconds of preparation of the solution. Below this concentration range the times required for formation of the two layers extend into hours, and are shown by the full line in Fig. 2, determined at 15°. The upper (broken) part of the curve has not been determined with the same degree of accuracy, but lies approximately in the position shown. It appears that if the system could be restricted to two components, *i.e.*, diethylammonium nitrate and liquid dinitrogen tetroxide, there would be no miscibility gap, but the immiscibility arises from the formation of further components in the solution owing to chemical reaction. Consistently with this, the position of the miscibility curve (Fig. 2) on the time axis is influenced considerably by variations in temperature.

Although freshly prepared solutions of diethylammonium nitrate have a negligible electrical conductivity, the solution becomes highly conducting on standing. The specific conductivity of an 11·5% solution (originally $<5 \times 10^{-6}$ ohm^{-1} cm.$^{-1}$) kept at 0°, increased to $1{\cdot}7 \times 10^{-4}$ ohm^{-1} cm.$^{-1}$ after 45 minutes, and to $2{\cdot}5 \times 10^{-4}$ ohm^{-1} cm.$^{-1}$ after 24 hours. A study of the reaction products in the light of the dinitrogen tetroxide solvent system therefore becomes of further importance since in spite of the low dielectric constant of dinitrogen tetroxide (Part IV, preceding paper) the products of reaction are highly conductive even in dilute solution.

Products of reaction. Diethylammonium salts and nitrosyl chloride react in the accepted manner (Sidgwick, " The Organic Chemistry of Nitrogen," Oxford Univ. Press, 1937, p. 24) to give diethylnitrosamine. This reaction occurs if the products of the solvolysis reaction (equation 1) are heated further, without preliminary removal of the nitrosyl chloride:

$$NOCl + Et_2NH_2NO_3 \longrightarrow Et_2N{\cdot}NO + HCl + HNO_3 \quad . \; . \; . \; . \; (2)$$

The usual laboratory method for the preparation of diethylnitrosamine from nitrous acid in aqueous solution follows a similar course

$$NO{\cdot}OH + Et_2NH_2Cl \longrightarrow Et_2N{\cdot}NO + H_2O + HCl \quad . \quad . \quad . \quad . \quad (3)$$

If dinitrogen tetroxide can be regarded as reacting as a nitrosyl compound ($NO{\cdot}NO_3$), the reaction with diethylammonium nitrate would be expected to follow a similar course :

$$NO{\cdot}NO_3 + Et_2NH_2NO_3 \longrightarrow Et_2N{\cdot}NO + 2HNO_3 \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Experiment has shown that this is indeed the case, and analysis indicates that the reaction proceeds quantitatively.

It is well known that reaction (3) may proceed in the reverse direction by boiling diethylnitrosamine with aqueous hydrochloric acid under reflux; the reaction $(Et_2NH_2)Cl + NOCl \longrightarrow Et_2N{\cdot}NO + 2HCl$, which resembles reaction (2) above, is also reversible, and may be used for the quantitative determination of diethylnitrosamine provided that the nitrosyl chloride is removed from the system. In the investigation of equation (4), liquid dinitrogen tetroxide was added to an excess of the nitrate, and the mixture kept in a sealed tube at room temperature. After it had stood for periods up to one week, 20—30% of the tetroxide could be recovered from the mixture, and reaction (4) appeared to proceed to an equilibrium. It is therefore probable that under appropriate conditions this reaction is also fully reversible.

Previous experiments (Part I, *loc. cit.*) have indicated that in its reaction with ionic compounds, heterolytic dissociation of the N_2O_4 molecule into NO^+ and NO_3^- ions is the significant feature, as opposed to the alternative (NO_2^+–NO_2^-) dissociation in reactions with covalent molecules; reaction (4) is consistent with this generalisation. However, it is not implied that the products of reaction are necessarily ionic. In reaction (1) the nitrosyl chloride produced has no more than 50% ionic character (Ketelaar and Palmer, *J. Amer. Chem. Soc.*, 1937, **59**, 2629); in reaction (4) the nitric acid produced in solution in dinitrogen tetroxide will give rise to ions (Goulden and Millen, *loc. cit.*), but the diethylnitrosamine is unlikely to have, *per se*, any appreciable degree of ionic character, although solutions of this compound in dinitrogen tetroxide show considerable electrical conductivity * (Part VI, following paper).

The significance of the nitrosamines in the dinitrogen tetroxide solvent system may be illustrated by consideration of the three equations

$$HOH + Et_2NH_2OH \rightleftharpoons [Et_2NH + HOH] + HOH \quad . \quad . \quad . \quad . \quad (5)$$

$$NO{\cdot}NO_3 + Et_2NH_2NO_3 \rightleftharpoons [Et_2N{\cdot}NO + HNO_3] + HNO_3 \quad . \quad . \quad . \quad (6)$$

$$NO{\cdot}NO_3 + \left[Et_2N\begin{matrix}\diagup NO \\ \diagdown NO\end{matrix}\right]NO_3 \rightleftharpoons [Et_2N{\cdot}NO + NO{\cdot}NO_3] + NO{\cdot}NO_3 \quad . \quad . \quad (7)$$

In a complete formal analogy between reactions involving amine salts in water and in liquid dinitrogen tetroxide, the replaceable H atoms should be replaced by the NO group, and the OH group by the NO_3 group. Aqueous solutions of ammonia or amines are known to contain free ammonia or amine molecules in equilibrium with the hydroxides; this equilibrium can be represented as in equation (5), and the complete analogy on the dinitrogen tetroxide solvent system is represented by equation (7).

Freezing-point curves for aqueous solutions of diethylamine show that several hydrates may exist (Pickering, *J.*, 1893, **63**, 141); the most pronounced peak occurs at an amine : water ratio of 2 : 1. Physical studies of solutions of diethylnitrosamine in liquid dinitrogen tetroxide described in Part VI (following paper) have shown that definite compound formation occurs, but clear evidence has been obtained for one ratio only (nitrosamine : N_2O_4 = 2 : 1). Other ratios may exist, but for the purpose of the formal analogy, the 1 : 1 ratio is employed in equations (5) and (7). Diethylnitrosamine may be regarded as the true analogue, in the dinitrogen tetroxide system, of the free base diethylamine in the aqueous system. Equation (6), which is treated experimentally in this paper, is then seen to represent a half-way stage between the two true solvent reactions (5) and (7), since the OH group in diethylammonium hydroxide is replaced by the NO_3 group, but the two replaceable hydrogen atoms remain. In consequence, nitric acid instead of dinitrogen tetroxide is produced, but the reaction may be regarded as involving the conversion of the free base (on the aqueous system) into the true free base on the dinitrogen tetroxide system.

* The maximum electrical conductivity reached by a solution of diethylammonium nitrate on long standing is greater than that of a solution containing an equivalent quantity of diethylnitrosamine.

Experimental.

The alkylammonium chlorides used were B.D.H. materials recrystallised from alcohol–ether and dried *in vacuo* over phosphoric oxide. The tetramethylammonium chloride was prepared by shaking a solution of the pure iodide in aqueous alcohol with excess of freshly precipitated silver chloride. The filtered solution was evaporated on a water-bath, and the crystals of chloride dried for 3 days over phosphoric oxide. The reactions between the chlorides and liquid dinitrogen tetroxide were carried out in 10 × 1·5 cm. test-tubes having B 14 ground-glass joints. The tube containing a sample of the chloride was attached by ground joints to the condenser containing freshly prepared dinitrogen tetroxide (Part II, *J.*, 1949, S 218), and the liquid poured from the condenser into the tube within a closed system and in the absence of moist air. When solutions of the corresponding nitrates were required for the preliminary study of solubility and miscibility, they were obtained from the chlorides as described below.

Reaction between Diethylammonium Chloride and Liquid Dinitrogen Tetroxide.—The reaction was carried out as above, and the products were identified as follows: (a) *Diethylammonium nitrate.* Removal of the nitrosyl chloride and dinitrogen tetroxide under reduced pressure gave a very pale yellow solid, which was washed with dry ether to remove traces of nitrosamine, nitric acid, and occluded dinitrogen tetroxide, then recrystallised from absolute alcohol. Qualitative tests indicated diethylammonium nitrate and the product had m. p. and mixed m. p. 102°. (b) *Nitrosyl chloride.* Although the odour, and colour in solution, were characteristic of nitrosyl chloride, it was possible that other volatile chlorine compounds (*e.g.*, nitryl chloride) were present. The volatile products removed from the reaction mixture were therefore condensed in a trap cooled to −15°, and the chloride content and m. p. of the condensate determined by the methods described in Part II (*loc. cit.*). The chlorine content was 7·13%. This is equivalent to a nitrosyl chloride content of 13·2% if all the chlorine was present in this form. On warming the condensate, the last crystals disappeared at −17·2°. When this m. p. was plotted on the NOCl–N_2O_4 phase diagram (Fig. 3, Part II, *loc. cit.*) it was found to lie on the liquidus curve for that system, and the condensate therefore contained only nitrosyl chloride and dinitrogen tetroxide.

The reaction was established quantitatively as follows: (a) *Diethylammonium nitrate.* 0·95 G. of the chloride was treated with about 4·5 g. of liquid dinitrogen tetroxide at −10°. The reaction mixture was then evaporated to dryness at 25—30°, and brown fumes were removed from the reaction tube by vacuum. After being washed with dry ether, the resulting solid was dried to a constant weight of 1·18 g., which is the theoretical yield for complete conversion of diethylammonium chloride into the nitrate. Since the reaction was completed within a few minutes, the quantity of nitrosamine produced was negligible. (b) *Nitrosyl chloride.* In a second experiment, 1·095 g. of the chloride were treated with about 5 g. of liquid dinitrogen tetroxide at −10°. The mixture was warmed slowly to 30°, and the gases evolved were bubbled into a bead-packed absorption tube containing 2N-potassium hydroxide. When all the nitrosyl chloride had been removed from the reaction mixture, the alkaline solution was acidified with nitric acid and boiled with a little hydrazine sulphate to destroy nitrite. Gravimetric analysis of this solution gave 0·352 g. of chlorine, equivalent to 0·650 g. of nitrosyl chloride. The theoretical yield of nitrosyl chloride [equation (1)] is 0·655 g.

Preparation of Diethylammonium Nitrate.—Appreciable quantities of this compound, in a pure dry state, were required for the experiments described in this and later papers. The following technique was found suitable. 20 G. of diethylammonium chloride were added to about 30 ml. of liquid dinitrogen tetroxide in a two-necked flask. One neck was fitted with an inlet tube passing below the liquid surface, and the other (outlet) neck was protected by a calcium chloride drying tube. Nitrosyl chloride was then eliminated by passing a stream of dry nitrogen through the liquid until the red colour gave way to the characteristic amber of the tetroxide. When the reaction was complete (*i.e.*, when a few ml. of the evolved gases when hydrolysed gave no test for chloride), excess of dry ether was added to the paste-like mass remaining, and the nitrate was precipitated as glistening plates. The product was filtered off, and washed again with ether to remove any traces of diethylnitrosamine. The nitrosyl chloride and dinitrogen tetroxide were removed as rapidly as possible from the reaction mixture in order to reduce the extent to which the subsequent reaction (forming diethylnitrosamine) could occur.

Reaction between Diethylammonium Nitrate and Liquid Dinitrogen Tetroxide.—(a) *Change in physical properties of solutions.* Changes in the freezing point of these solutions over long periods of time (Fig. 1) were determined by sealing known quantities of the two components in glass tubes, and observing the freezing point by the thaw–melt method. Similar tubes, kept in a thermostat at 15°, were employed to observe the appearance of a second liquid phase (Fig. 2).

(b) *Products of reaction.* About 6 g. of liquid dinitrogen tetroxide were poured, in a closed system and in the absence of moist air, into a 10 × 1·5 cm. Pyrex glass tube (drawn out to a constriction immediately below the ground joint) containing excess (about 10 g.) of dry diethylammonium nitrate. The tube was then separated from the tetroxide container, and a phosphoric oxide guard tube fitted to the ground joint. The lower portion of the tube was surrounded by pieces of solid carbon dioxide, and the tube sealed at the constriction as soon as the contents had solidified. The reaction was then allowed to proceed at room temperature. During the first day, the contents of the tube changed from a "moist" solid to a yellow liquid containing a small quantity of undissolved solid. About two days were required for the disappearance of all crystals. As the reaction progressed, the colour of the liquid changed from deep yellow to olive-green; the green colour arises from a slight side reaction (discussed in the following paper) which does not occur to a sufficient extent to be relevant here. The tube was set aside for one week before being opened. It was then placed in a stout glass-stoppered bottle containing 250 ml. of dry ether, and the bottle was shaken, so that the tube broke, the excess diethylammonium nitrate was precipitated, leaving an orange-coloured supernatant liquid. The analysis was carried out as follows:

(1) 25 Ml. of the liquid were withdrawn by use of a guarded pipette, and run under the surface of an excess of approximately 2N-potassium hydroxide solution held in a separating funnel. After shaking,

the aqueous layer was run off and the nitrite content determined by means of standard hydrazine sulphate solution (Mellan, "Organic Reagents in Inorganic Analysis," Blakiston Co., Philadelphia, 1941, p. 488). The usual method for nitrite estimation employing potassium permanganate solution is invalidated by the presence of diethylnitrosamine. From the nitrite content, the quantity of unchanged dinitrogen tetroxide in the reaction mixture was calculated.

(2) A further 50-ml. portion of the ethereal solution was transferred to a stoppered flask and evaporated at room temperature under reduced pressure to about half the volume; this removed unchanged dinitrogen tetroxide, as shown by fading of the orange colour to very pale yellow. A stream of dry air-borne ammonia gas was then aspirated through the ethereal solution, and a flocculent white precipitate was formed. When precipitation was complete, the solid was filtered off, washed with dry ether, and weighed. Analysis showed it to be pure ammonium nitrate, and from its weight, the quantity of nitric acid produced in the reaction was calculated.

(3) The filtrate and ether washings from the ammonium nitrate precipitation were evaporated under reduced pressure at about 0° until all the ether was removed. The pale yellow liquid remaining was weighed, and characterised as pure diethylnitrosamine (b. p. 174—176°). The weight of nitrosamine was corrected for that lost during the evaporation of the ether, by carrying out blank experiments with ether–nitrosamine mixtures of known concentration.

(4) The unreacted diethylammonium nitrate which was precipitated from the original ether solution on breaking the reaction tube, was filtered off, washed with dry ether, and weighed.

Three separate experiments were carried out, and the results, given in the following table, confirm that the reaction between diethylammonium nitrate and liquid dinitrogen tetroxide proceeds almost entirely in accordance with equation (4).

	G.-mols. reacting with, or produced from, 1 g.-mol. of $Et_2NH_2NO_3$.		
Expt. no.	N_2O_4 reacted.	$Et_2N{\cdot}NO$ produced.	HNO_3 produced.
1	1·31	1·13	2·19
2	0·95	0·82	1·91
3	0·95	0·95	1·94

THE UNIVERSITY, NOTTINGHAM. [*Received, December 16th*, 1950.]

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289. *The Liquid Dinitrogen Tetroxide Solvent System. Part VI. Thermal and Conductometric Studies of Solutions of Diethylnitrosamine in Liquid Dinitrogen Tetroxide.*

By C. C. ADDISON, C. P. CONDUIT, and R. THOMPSON.

Thermal and conductometric measurements carried out over the full concentration range show that liquid dinitrogen tetroxide and diethylnitrosamine undergo compound formation, and that the state of the liquid mixtures may be represented by the equilibria

$$N_2O_4 + nEt_2N{\cdot}NO \rightleftharpoons N_2O_4.nEt_2N{\cdot}NO \rightleftharpoons \text{ionic dissociation products}$$

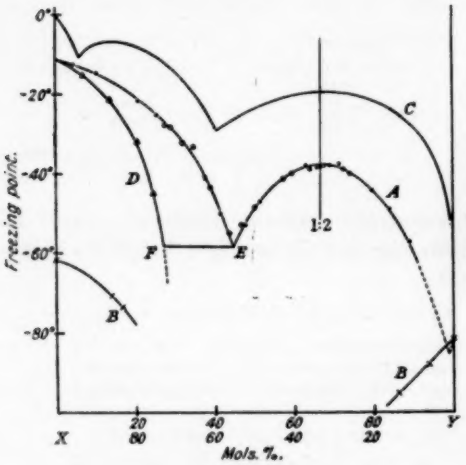
Freezing-point data show that at low temperatures the compound $N_2O_4.2Et_2N{\cdot}NO$ is predominant; the positions of the maxima on the conductivity and heat evolution curves of the mixtures suggest that compounds involving other molecular ratios may exist. The compound (or compounds) formed undergo sufficient ionic dissociation to give rise to a maximum specific conductivity of $3{\cdot}5 \times 10^{-4}$ ohm^{-1} cm.$^{-1}$ (at 0°) at the composition equivalent to $N_2O_4.2Et_2N{\cdot}NO$. Molecular-weight values determined from cryoscopic data are consistent with appreciable ionic dissociation. The cryoscopic constant of liquid dinitrogen tetroxide has been redetermined as 3·64.

IN Part V (preceding paper) it was suggested that diethylnitrosamine may have significance as a "free base" in the liquid dinitrogen tetroxide solvent system. Its solutions have been found to possess certain properties which are not inconsistent with this concept (such as reactions with metals to give soluble compounds, discussed in a later paper); for this reason, together with the fact that diethylnitrosamine is produced in solutions of diethylammonium nitrate, it became necessary to determine some of the properties of solutions of diethylnitrosamine in liquid dinitrogen tetroxide. The properties described in this paper are considered in four sections: (1) phase diagram, (2) conductometric analysis of the solutions, (3) molecular-weight determinations, and (4) heats evolved on mixing the two components.

(1) *Freezing Points of Solutions.*—The liquidus curve for solutions of diethylnitrosamine in liquid dinitrogen tetroxide is shown in Fig. 1 (curve *A*). On addition of diethylnitrosamine to

the tetroxide, the freezing points fall smoothly to a eutectic (*E*) at 44·5 mols. % of diethylnitrosamine and −58°. No breaks in the curve which might indicate compound formation were detected in this concentration range. At concentrations above 44·5 mols. %, the freezing-point curve passes through a maximum at −37·5°, and at a dinitrogen tetroxide : diethylnitrosamine ratio of 1 : 2. Thereafter the curve falls towards the freezing point of pure diethylnitrosamine which has been found to be −81°. Although accurate freezing points were not determined for diethylnitrosamine concentrations above 90 mols. %, the shape of the curve is probably as shown by the broken portion of curve *A*, with a second eutectic close to the diethylnitrosamine axis. Curve *A* therefore provides evidence for the formation of a compound of formula $N_2O_4.2Et_2N{\cdot}NO$. The shape of the maximum, and the width of this portion of the curve, suggest that the compound should have an appreciable stability, although the maximum is not sufficiently sharp to exclude the possibility of some dissociation. This curve, together with the conductometric measurements reported below, indicates that there is considerable interaction between the two components in the liquid state. It is probable, therefore, that the maximum in curve *A* (Fig. 1) reflects the formation of a chemical, rather than a lattice, compound.

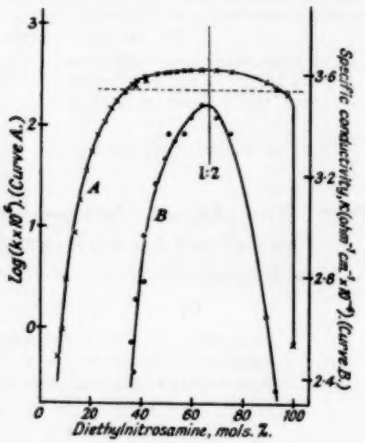
FIG. 1.



Components :

Curve.	*X.*	*Y.*
A	*Dinitrogen tetroxide.*	*Diethylnitrosamine.*
B	*Nitrosyl chloride.*	*Diethylnitrosamine.*
C	*Water.*	*Diethylamine.*

FIG. 2.



(Curve B represents the portion of Curve A above the broken line, regraphed on a linear scale.)

On a formal analogy with the aqueous system, the solution of diethylnitrosamine in dinitrogen tetroxide is equivalent to a solution of diethylamine in water. The freezing points of this latter system are reproduced, from Pickering's results (*J.*, 1893, **63**, 141), as curve C, Fig. 1. Various minor fluctuations in the freezing-point values on the left-hand side of the eutectic, which Pickering considered to represent additional compounds, have been omitted in drawing the smooth curve *C*. It is of interest that over the 20—100 mols. % concentration range the curves are closely similar; the major feature in each curve is the occurrence of a maximum at the 1 : 2 mol. ratio.

Diethylnitrosamine and dinitrogen tetroxide form solid solutions. For the purpose of the molecular-weight measurements discussed below, part of the solidus curve has been determined experimentally, and is shown as curve *D* in Fig. 1 (cf. the corresponding nitrosyl chloride–dinitrogen tetroxide phase diagram, Part II, *J.*, 1949, S 218). A somewhat unusual effect was observed on cooling solutions containing about 40 mols. % of diethylnitrosamine (*i.e.*, slightly below the eutectic concentration). When the liquid was cooled, solid crystallised continuously from the liquid phase; on reaching the eutectic temperature (−58°), no thermal arrest occurred in spite of the fact that an appreciable proportion of solid phase was present. The liquid could

be cooled through a further 10°; at about −68° the whole mass solidified, and the temperature returned sharply to the eutectic value. In the temperature range −58° to −68° the liquid therefore appears to be supercooled with respect to some solid other than that represented by a saturated solid solution of diethylnitrosamine (or the 1 : 2 compound) in dinitrogen tetroxide (point *F*). A full investigation of the solidus systems involved here was outside the scope of the present work; however, the liquid may be supersaturated below −58°, with respect to the second eutectic solid, which would represent (by a point to the right of *E*) a saturated solid solution of dinitrogen tetroxide in the 1 : 2 compound. The phenomenon may then be explained by assuming continued crystallisation along curve *D* and beyond *F*, until the lattice becomes so strained that it breaks down into the two eutectic solids, with an accompanying rise in temperature to the true eutectic value.

For purposes of comparison, an attempt was made to obtain the phase diagram for the system diethylnitrosamine–nitrosyl chloride. At concentration ranges up to about 20 mols. % of either component in the other, the solutions crystallised normally, with little supercooling. Freezing points are represented by curves *B*, Fig. 1. In the concentration range 20—80 mols. %, supercooling occurred, accompanied by a considerable increase in viscosity. These solutions crystallised with difficulty; they were so viscous that efficient stirring was not possible, and accurate freezing points could not be determined. The approximate values obtained indicated that the liquidus curves fall to a simple eutectic at about 55 mols. % of diethylnitrosamine, and a temperature of −130°, with no evidence of compound formation.

(2) *Conductivity Measurements.*—The specific conductivities of mixtures of diethylnitrosamine and liquid dinitrogen tetroxide have been determined at 0° over the full concentration range, and the values are given in Fig. 2 (curve *A*). On addition of diethylnitrosamine to the liquid tetroxide, the specific conductivity undergoes a considerable increase, from $1{\cdot}3 \times 10^{-13}$ ohm^{-1} cm.$^{-1}$ for the pure liquid tetroxide (Part III) to a maximum of $3{\cdot}5 \times 10^{-4}$ ohm^{-1} cm.$^{-1}$. However, the increase in conductivity occurs much more rapidly on addition of dinitrogen tetroxide to the diethylnitrosamine. The best value for the specific conductivity of pure diethylnitrosamine (achieved by repeated distillation under reduced pressure) was $5{\cdot}4 \times 10^{-7}$ ohm^{-1} cm.$^{-1}$. In order to prepare dilute solutions of the tetroxide in diethylnitrosamine for conductivity measurement, the latter was placed in the conductivity cell (Fig. 4) and the liquid tetroxide poured in by the usual closed-system technique. It was observed that during this process the conductivity of the diethylnitrosamine increased more than 100-fold immediately after contact with the tetroxide vapour, *i.e.*, before any liquid tetroxide was actually added. The quantity of tetroxide required to bring about this considerable increase in conductivity was too small to be measurable with accuracy, and in consequence the specific conductivity of the mixture is shown in Fig. 2 (curve *A*) as rising almost vertically from the diethylnitrosamine value.

It would appear from the logarithmic plot of the specific conductivity (curve *A*) that the conductivity curve possesses a broad, flat maximum extending over the 50—80 mols. % diethylnitrosamine range. However, the conductivity measurements are of sufficient accuracy to enable the values to be plotted on a linear scale over this concentration range (curve *B*). The specific conductivity is then seen to pass through a fairly sharp maximum, at a composition corresponding to that of the compound $N_2O_4{,}2Et_2N{\cdot}NO$. Although the general chemistry of dinitrogen tetroxide and diethylnitrosamine suggests that neither of these molecules is likely to undergo appreciable ionisation separately, the conductivity measurements indicate that they combine to form a 1 : 2 compound which is capable of considerable ionic dissociation.

The general form of the conductivity curve *A* may be interpreted on the basis of the dielectric constants of the two liquids. Liquid dinitrogen tetroxide has been shown to have a low dielectric constant (2·42; Part IV, *J.*, 1951, 1294). The structure of the dialkylnitrosamines might be expected to give rise to high dielectric-constant values for the pure liquids. The Raman spectra (Barredo and Goubeau, *Z. anorg. Chem.*, 1943, **251**, 2; Wittek, *Anz. Akad. Wiss. Wien, Math.-Naturw. Klasse*, 1943, 5; *Chem. Zentr.*, 1943, ii, 1701) for the dimethyl compound have been interpreted on the basis of the resonance states $Me_2N{-}N{=}O$ and $Me_2N^{+}{=}N{-}O^{-}$. If the latter state makes an appreciable contribution to the structure of the diethyl compound also, this liquid should possess dipolar character. The dielectric constant for diethylnitrosamine has therefore been determined experimentally, and found to be 42·5 at 22°; this is of the same order as the value (53·3) obtained for dimethylnitrosamine by Walden (*Z. physikal. Chem.*, 1903, **46**, 103).

The compound formed on the addition of small quantities of diethylnitrosamine to liquid dinitrogen tetroxide will be dissolved in a medium consisting mainly of dinitrogen tetroxide, and

therefore of low dielectric constant. The ions produced by dissociation of the compound will, in consequence, exist predominantly in the form of ion-pairs, which make no contribution to the conductivity. The addition of further quantities of diethylnitrosamine will increase the amount of compound present, and will also increase the dielectric constant of the medium, with consequent increase in the proportion of free ions to ion-pairs. On the other hand, the compound when formed by addition of a small quantity of dinitrogen tetroxide to a large excess of diethylnitrosamine is dissolved in a medium of high dielectric constant, in which the compound is able to dissociate into free ions. It was therefore to be expected that the increase in conductivity would be more rapid on the diethylnitrosamine than on the dinitrogen tetroxide side of the conductivity curve (Fig. 2, curve *A* or *B*). A further factor may contribute to the rapid rise in conductivity on adding small quantities of tetroxide to diethylnitrosamine. Goulden and Millen (*J.*, 1950, 2620) have shown, from studies of Raman spectra of the solutions, that in dilute solution in pure nitric acid, dinitrogen tetroxide is almost completely dissociated, and that the dissociation occurs mainly heterolytically into the NO^+ and NO_3^- ions. If similar ionisation occurs in solution in diethylnitrosamine, then this fact may in itself contribute towards the rapid rise in electrical conductivity.

The two concepts discussed above may be closely complementary. The formation of ionic species may be considered to arise either (*a*) from the formation of a compound $N_2O_4,2Et_2N{\cdot}NO$, which undergoes ionic dissociation in solution in diethylnitrosamine, or (*b*) from ionisation of dinitrogen tetroxide, aided by the ability of one of the ions (*e.g.*, the nitrosonium ion) to form a molecular compound with the diethylnitrosamine.

The broad maximum on the conductivity curve may arise from at least three factors. (*a*) Further addition of diethylnitrosamine to the 1 : 2 compound decreases the concentration of ionisable compound, but the increase in dielectric constant will increase the degree of ionisation, and will thus tend to maintain the high conductivity value. (*b*) With changing concentration there may also be a displacement of the equilibrium between the compound and its constituents. Nitrogen dioxide could be observed in the atmosphere above the liquid mixtures at all concentrations; it is possible to displace the equilibria in the equation given below entirely to the left-hand side, since dinitrogen tetroxide may be removed quantitatively from the system by evaporation under reduced pressure. (*c*) The results in Fig. 2 do not exclude the possibility of association of the two components in the liquid state in other simple ratios, since the conductivity has almost its maximum value at the 1 : 1 ratio. The equilibria concerned in this system may therefore be represented as follows:

$$N_2O_4 + n\mathrm{Et_2N{\cdot}NO} \rightleftharpoons N_2O_4,n\mathrm{Et_2N{\cdot}NO} \rightleftharpoons \text{ionic dissociation products}$$

Although no quantitative measurements of the temperature coefficient of conductivity have been made, it was observed that the electrical conductivity of these liquid mixtures increased with increasing temperature over the full concentration range.

(3) *Cryoscopic Constant.*—The cryoscopic constant of liquid dinitrogen tetroxide was determined by Ramsay (*J.*, 1890, **57**, 590). In view of the experimental technique involved, the results were only approximate, and it was considered desirable to redetermine this value. The measurements were carried out by using a simple Beckmann method; the solute was added, by means of a weight pipette, through a side arm in the melting-point tube with precautions to avoid contact with the atmosphere. Duplicate values for the cryoscopic constant (K_f), obtained by using three different solutes, are compared with Ramsay's values below:

	K_f (degrees/g.-mol./1000 g. solvent).	
Solute.	Present work.	Ramsay (*loc. cit.*).
$CHCl_3$	3·69, 3·64	4·10
C_6H_5Cl	3·57, 3·53	4·166
CCl_4	3·73, 3·65	—
	Mean value = 3·64.	

The mean value is significantly lower than Ramsay's value. From the relation $K_f = RT_f^2M/1000L$, and with the values $T_f = 261{\cdot}9°$ K., $L = 3502$ cals./g.-mol. (Giauque and Kemp, *J. Chem. Physics*, 1938, **6**, 40), the calculated cryoscopic constant is 3·58, in close agreement with our measured value. Ramsay (*loc. cit.*) made a similar comparison, and observed that the latent heat of fusion measured experimentally (32·6 cals./g.) was close to the value (33·7 cals./g.) calculated by assuming $K_f = 4{\cdot}1$. However, this agreement is coincidental, since the experimental determination of L involved the use of values for the specific heats of liquid and solid dinitrogen tetroxide which were incorrect, and which Ramsay considered to be unreliable.

It is of interest that the mean value for the molecular weight of dinitrogen trioxide dissolved in dinitrogen tetroxide, found by Ramsay to be 84·9 on the basis of $K_f = 4·10$, becomes 75·4 (*i.e.*, almost the theoretical value for the N_2O_3 molecule) when K_f is adjusted to 3·64.

Molecular-weight Determination.—Experiments described above show that the compound which diethylnitrosamine forms with liquid dinitrogen tetroxide appears to be capable of ionic dissociation. In order to elucidate further the nature of these solutions, an attempt has been made to determine the molecular weight of diethylnitrosamine in dilute solution in liquid dinitrogen tetroxide, Beckmann's method of freezing-point depression being used. Fig. 1 shows that diethylnitrosamine has a considerable solubility in solid dinitrogen tetroxide. In view of the assumptions which have, in consequence, to be made, it is not necessary to employ, in the calculation of molecular weights, a treatment more refined than that represented by the equation $M = K_f \omega (1 - k)/\Delta T$, where ω is the weight of diethylnitrosamine in 1000 g. of the tetroxide, and k represents the ratio of the mol.-fraction of the solute in solid to that in liquid dinitrogen tetroxide. The following results show the ΔT values obtained for three concentrations of diethylnitrosamine.

ω, g.	29·47	44·61	48·76
ΔT	0·88°	1·37°	1·53°

It has been assumed, for the present purpose, that (*a*) when diethylnitrosamine is added to the tetroxide it forms the compound $N_2O_4.2Et_2N·NO$ (the weights of added diethylnitrosamine have been adjusted on this basis); (*b*) k represents the ratio of the concentration of this compound in the solid to that in the liquid, irrespective of any dissociation which this compound may undergo in the liquid state.

Expressed as a ratio of the mol.-fraction of compound, k varies with total concentration. However, the position of the liquidus and solidus curves in Fig. 1 show that if k should be expressed as the ratio of the concentration of diethylnitrosamine itself in the solid and the liquid phases, then its value is independent of concentration, within experimental error, over the 0—45 mol. % diethylnitrosamine concentration range.

If the two alternative definitions of k be termed k_1 and k_2, respectively, then the value of k_1 is found to approach the constant value k_2 with decreasing diethylnitrosamine concentration, so that in the dilute solutions used in the cryoscopic measurements a value of k, sufficiently accurate for present purposes, may be obtained from the mean of the values of k_2 read directly from Fig. 1. The following table shows the variation, and constancy, of k_1 and k_2, respectively, with change in concentration.

If k is assigned the value 0·625, the results from ω and ΔT (above) give a value of 59 for the molecular weight of the dissolved compound, compared with the theoretical value of 296 in the absence of dissociation.

$Et_2N·NO$, total mol. %	10·7	19·0	25·4	30·4	34·2	37·1	39·7	41·5	44·5
k_1	0·600	0·590	0·570	0·545	0·520	0·515	0·495	0·490	0·465
k_2	0·625	0·630	0·640	0·630	0·620	0·625	0·620	0·620	0·610

In view of the assumptions necessary at this stage, and until further evidence on the nature of the dissociation is available, the molecular weight value of 59 cannot be assumed to have any detailed significance. These results, however, support the belief that a considerable degree of dissociation in solution does occur. Electrolytic and other experiments, designed to determine the precise nature of the ionic species, are in hand.

(4) *Heats of Mixing.*—Although the addition of soluble salts to liquid dinitrogen tetroxide produces no appreciable temperature changes, the addition of diethylnitrosamine produces an immediate increase in temperature which may be as much as 20°. Since this heat evolution is probably due, at least in part, to compound formation, and since the quantities of heat are sufficiently large to permit measurements of some accuracy, this heat evolution (expressed as the heat evolved in the preparation of 10 g. of the mixture) has been measured over the concentration range, and the results are shown in Fig. 3. The curve has a rounded maximum; although freezing-point and conductivity data (Figs. 1 and 2) showed maxima at the composition corresponding to the compound $N_2O_4.2Et_2N·NO$, this is not the case with the thermal measurements where the maximum falls between the 1 : 1 and 1 : 2 molecular ratios. This may result from the following factors.

(*a*) The measured heat changes, although they probably arise predominantly from the heat of compound formation, will include other thermal effects, amongst which the heat of ionisation of the compound may be significant. With changing concentration, the compound is produced

in media of differing dielectric constant. In consequence, the heat of ionisation will not be a constant factor, and may give rise to a displacement of the maximum.

(*b*) The position of the maximum could arise from the presence, in the mixture, of both the 1 : 1 and the 1 : 2 compound in equilibrium. This is not inconsistent with previous observations. The freezing-point data, at temperatures about −40°, showed the presence of the 1 : 2 compound only. However, the conductivity of a 1 : 1 mixture (determined at 0°) was almost as great as that of the 1 : 2 mixture. These results are all in accord with the postulate

FIG. 3.

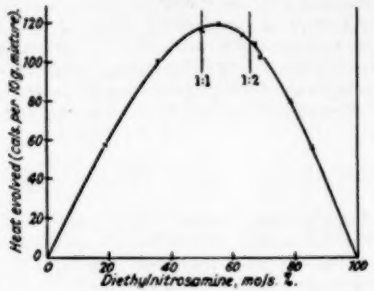


FIG. 4.

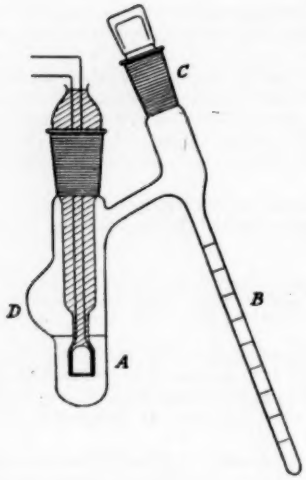
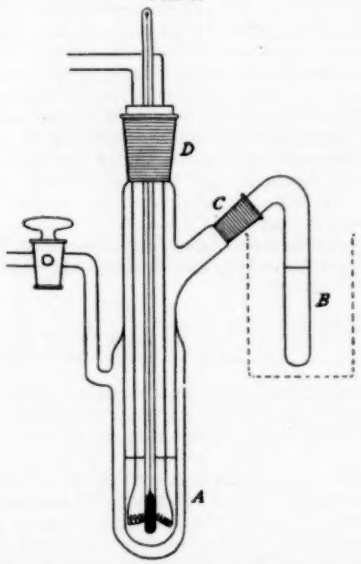


FIG. 5.



that in these liquid mixtures an equilibrium exists between the 1 : 1 and the 1 : 2 compound, and that this equilibrium is displaced towards the 1 : 1 compound with increasing temperature.

During the course of the calorimetric measurements, opportunity was taken to determine the specific heats of the mixtures, and of pure diethylnitrosamine. The values given below were determined over the range 0—15°, with an accuracy of ±0·005 cal./g.

Diethylnitrosamine, mols. %	19·0	35·3	50·2	55·4	60·1	62·8	67·3	68·7	78·6
Specific heat (cals./g.)	0·410	0·450	0·450	0·460	0·470	0·470	0·465	0·465	0·455

The value determined for pure liquid dinitrogen tetroxide was close to the value (0·362 cal./g. at 7°) reported by Giauque and Kemp (*loc. cit.*). The specific heat of pure diethylnitrosamine

was found to be 0·452 cal./g. (mean of four determinations 0·448, 0·457, 0·454, 0·449). The specific-heat values of the mixtures pass through a maximum at a concentration close to that at which the maximum heat evolution occurs.

Further Reaction between Diethylnitrosamine and Liquid Dinitrogen Tetroxide.—Over periods of time up to about 12 hours there is no detectable reaction between the two liquids other than the reversible reactions discussed above. However, over periods of days a further and apparently irreversible reaction occurs. When liquid mixtures containing about 30—50 mols. % of diethylnitrosamine were sealed into stout glass tubes, the liquid changed in colour through brown-green to a clear olive green within 1—2 days, and to a deep green-black within 3—4 days. A pressure of gas was generated inside the tube, sufficient in some cases to burst the tube after 2—3 weeks' standing at room temperature. Preliminary analyses of the contents of the tube after 6—7 days indicate that the extent of the reaction is slight, since at least 95% of the original reactants could be recovered. When the tube contents were fractionally distilled, the dinitrogen tetroxide was first removed, leaving a red liquid. On further heating, the red colour faded to the pale yellow colour of diethylnitrosamine, and a trace of a colourless liquid boiling slightly below 100° distilled off. The distillation temperature then rose rapidly to the boiling point of diethylnitrosamine. The reaction probably involves oxidative degradation, with the liberation of nitric oxide. The reaction was not investigated further, since it has so significance in freshly prepared solutions, and does not interfere in any way with the measurements reported in this paper.

Experimental.

Preparation of Materials.—Dinitrogen tetroxide and nitrosyl chloride were prepared as described in Part II (*loc. cit.*). Diethylnitrosamine was prepared from diethylammonium chloride and sodium nitrite (Vogel, "Textbook of Practical Organic Chemistry," Longmans, 1948, p. 417), and was redistilled immediately before use.

Freezing Points.—The f. p.s shown on curve *A* (Fig. 1) as black circles were obtained by the thaw-melt method. Weighed quantities of the two liquids were sealed into a glass phial; the phial was attached to a calibrated thermometer, and immersed in a bath of alcohol. The bath was cooled by solid carbon dioxide until crystals appeared, and then allowed to warm slowly, with stirring, to determine the temperature at which the crystals disappeared. F. p.s shown as open circles on curve *A* (Fig. 1) were obtained by the normal warming-curve technique, and agree closely with the others. To determine the f. p.s of nitrosyl chloride–diethylnitrosamine mixtures, the tube containing the liquid was surrounded by an air-jacket immersed in liquid oxygen, and the f. p.s again determined from warming curves. The solidus curve *D* was determined precisely as described for nitrosyl chloride [method (*b*), p. S 221, Part II].

Electrical Conductivity.—The cell used is shown in Fig. 4. A Mullard Cell Type G.M. 4221 was adapted for the purpose by removing the glass shield surrounding the electrodes (to facilitate the mixing of the liquids); a B 24 ground-glass cone was attached as shown to enable the limb *A* to be closed on insertion of the electrode assembly. The electrodes were platinised to increase the sensitivity with which the null point could be detected, and gave a cell constant of 2·43. Under these conditions there appeared to be little polarisation effect, since the measurements were not affected by a frequency change from 50 to 1000 c./s. The conductivity values were determined by using a Mullard Measuring Bridge Type G.M. 4140/1. A known quantity of pure diethylnitrosamine (about 10 g.) was distilled into limb *A* of the cell, and its conductivity measured in the absence of dinitrogen tetroxide vapour. The cell was then tilted to enable liquid dinitrogen tetroxide to be poured (in a closed system) *via* B 19 joint *C* into the limb *B* of the cell, which carried 0·1-ml. graduation marks. Liquid tetroxide was then poured, by tilting, from limb *B* into *A*, and the angle of limb *B* was so chosen with respect to limb *A* that, on tilting, the liquid surrounding the electrodes was held in the bulb *D* formed on the side of limb *A*. The temperature was kept at 0° by immersing the cell, to a level above the arm connecting limbs *A* and *B*, in a bath of melting ice. At this temperature no difficulties were encountered arising from the distillation of dinitrogen tetroxide from limb *B* into *A*, although at higher temperatures the possibility of errors from this source does arise. The 60—100 mols. % diethylnitrosamine range was covered by the above technique. Conductivities for the remainder of the concentration range were determined by pouring diethylnitrosoamine into either a known quantity of liquid dinitrogen tetroxide or a mixture of known composition.

Purification of Diethylnitrosamine.—The electrical conductivity of diethylnitrosamine is sensitive to traces of moisture, or impurity produced during distillation at atmospheric pressure. Some typical conductivity values obtained by different methods of purification are given below.

Expt.	Treatment.	κ (ohm^{-1} cm.$^{-1}$).
A	Successive distillation at 176°/760 mm.	(1) $1{\cdot}1 \times 10^{-6}$
		(2) $6{\cdot}3 \times 10^{-6}$
		(3) $4{\cdot}5 \times 10^{-6}$
B	Original product dried (Na_2SO_4) and distilled at 176°/760 mm.; redistilled at 176°/760 mm.; redistilled at 74°/24 mm.	(1) $1{\cdot}2 \times 10^{-6}$
		(2) $5{\cdot}6 \times 10^{-6}$
		(3) $1{\cdot}4 \times 10^{-6}$
C	Two distillations at 176°/760 mm. followed by one distillation at 36°/3 mm.; redistilled at 36°/3 mm.	(1) $2{\cdot}7 \times 10^{-6}$
		(2) $5{\cdot}4 \times 10^{-7}$

The conductivity values quoted were determined in all cases on the middle distillation fraction. Drying agents were found to be of little use in effecting ultimate drying of the diethylnitrosamine; sodium sulphate caused some decomposition. The material used throughout the conductivity measurements was purified by low-pressure distillation (expt. C). The electrical conductivity of dimethylnitrosamine is given by Walden (*loc. cit.*) as $2{\cdot}95 \times 10^{-8}$ ohm^{-1} cm.$^{-1}$ at 25°. It appears possible from the above that this value could be lowered appreciably by low-pressure distillation.

Dielectric Constant of Diethylnitrosamine.—The condenser and containing cell used were similar to those described in Part IV (*loc. cit.*). Because of the lower electrical resistance of diethylnitrosamine, and in order to adjust the capacity of the condenser to within the capacity range of the standard condenser, the annular distance between the concentric nickel cylinders was increased from 1 mm. to 3 mm. The measurement of capacity was carried out essentially as described in Part IV except that in place of the Mullard Capacity Bridge, the Marconi circuit magnification meter (*Q*-meter) was used as the detecting instrument in conjunction with a Muirhead standard variable air condenser. The sensitivity of the *Q*-meter falls considerably with decreasing resistance of the liquid between the condenser plates. With diethylnitrosamine purified as in Expt. C(2) (above), the resistance of the liquid between the plates was about 10,000 Ω. The *Q* value obtained at this resistance was about one-third of that obtained with infinite resistance (*i.e.*, air), but was sufficiently great to permit accurate detection of resonance in the circuit, over the frequency range 800 Kc./s. to 1·3 Mc./s. To calibrate the cell, pure nitrobenzene (redistilled at 48°/1·2 mm.) was used. Dielectric-constant measurements were carried out at 22°, and an ε value of 34·8 (interpolated from Lattey and Gatty's data, *Phil. Mag.*, 1929, **7**, 985) assumed for nitrobenzene at this temperature.

The total capacity of the cell was $16{\cdot}8 \pm 0{\cdot}3$ μμF. in air, $258{\cdot}7 \pm 2{\cdot}1$ μμF. in nitrobenzene, and $313{\cdot}5 \pm 1{\cdot}4$ μμF. in diethylnitrosamine, each result being derived from ten determinations. These results, together with the assumed ε value for nitrobenzene, give the dielectric constant of diethylnitrosamine as 42·5 at 22°; this value is considered to be accurate to $\pm 0{\cdot}7$ unit, which is adequate for the present purpose.

Heats of Mixing.—The heats of mixing, and specific heats, were determined by using the apparatus shown in Fig. 5. A weighed quantity of one of the components was placed in the main glass calorimeter tube *A*, and a weighed quantity of the second component in tube *B*. The liquid in both tubes was cooled to 0° in baths of melting ice. Preliminary experiments showed that the increase in temperature on mixing the liquids under these conditions was about 15°; tube *A* was therefore surrounded by a bath kept constant at about 7° and jacket *A* was evacuated to assist thermal insulation. Under these conditions the heat which the liquid in *A* gained from, or lost to, the surroundings was negligible during the short periods (not exceeding 1 minute) required for each measurement. With both liquids at 0°, tube *B* was rotated in the ground joint *C*, the liquid in *B* poured into *A*, and the increase in temperature observed with an accuracy of $\pm 0{\cdot}05$°. The thermometer was used as stirrer, and was held in joint *D* by a flexible silicone rubber plug, which also carried the leads to the heating coil. (Silicone rubber is not attacked by dinitrogen tetroxide vapour except after prolonged contact.)

The vacuum in the jacket *A* was released to enable the contents of tube *A* to be cooled rapidly to 0°. The vacuum was then restored, the tube replaced in the constant-temperature bath, and the quantity of electrical energy required to heat the liquid through the same temperature range was measured by using a simple battery–voltmeter–ammeter assembly in conjunction with the heating coil. In measuring the fall in potential across the heating coil, allowance was made for the resistance of the leads. The coil and leads were of Nichrome wire, thickness 30 and 18 S.W.G., respectively.

The specific heats of the mixtures were obtained from the electrical heating data, with allowance for the water equivalent of the apparatus. Because of the low thermal conductivity of glass, the water equivalent was found to vary with the volume of liquid in tube *A*, from 2·21 g. (for 10 ml. of mixture) to 3·80 g. (for 25 ml.). The water equivalent of the apparatus was therefore determined for a series of volumes between these limits using pure acetone.

THE UNIVERSITY, NOTTINGHAM. [*Received, December 16th*, 1950.]

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290. *Ferric Thiocyanate. Part I. Molecular Weight in Organic Solvents.*

By K. M. MITCHELL and J. Y. MACDONALD.

The molecular weight of ferric thiocyanate has been determined in ether and alcohol. Contrary to the results of Schlesinger and Van Valkenburgh, only the monomer, $Fe(CNS)_3$, is found to be present. The substance is not soluble in pure benzene.

As the result of investigation of the constitution of ferric thiocyanate Schlesinger and Van Valkenburgh (*J. Amer. Chem. Soc.*, 1931, **53**, 1212) considered that the substance was a dimer, $Fe_2(CNS)_6$, in organic solvents, dissociating in water to give the anion $Fe(CNS)_6^{3-}$. Their main evidence was ebullioscopic and cryoscopic measurements in ether and benzene, and electrical migration experiments in aqueous solution. In so far as the organic solvents are

concerned, this work seems to have been generally accepted (Baldwin and Svirbely, *ibid.*, 1949, **71**, 3326; Uri, *J.*, 1947, 336), but a number of workers (Møller, *Kem. Maanadsblad*, 1937, **18**, 138; Bent and French, *J. Amer. Chem. Soc.*, 1941, **63**, 568; Edmunds and Birnbaum, *ibid.*, p. 1471; Babko, *Compt. rend.* (*Doklady*) *Acad. Sci. U.R.S.S.*, 1946, **52**, 37; Frank and Ostwalt, *J. Amer. Chem. Soc.*, 1947, **69**, 1321) have since produced conclusive evidence for the existence of the ion $FeCNS^{2+}$ in dilute aqueous solution, and have measured its stability constant $K_1 = [FeCNS^{2+}]/[Fe^{3+}][CNS^-]$ at various ionic strengths.

That higher complexes also exist is shown by the fact that solvents such as ether can extract the red colour from aqueous ferric thiocyanate solutions (thus proving the existence of at least traces of a neutral complex $[Fe(CNS)_3]_x$) and by the fact that in certain solutions migration to the anode can occur (Babko, *loc. cit.*; Schlesinger, *loc. cit.*; *J. Amer. Chem. Soc.*, 1941, **63**, 1765), indicating negatively charged complexes. Babko has postulated a series of complexes of the type $Fe(CNS)_x^{(3-x)+}$, carrying $(3 - x)$ positive charges, where x varies from 0 to 6. He gives stability constants for these complexes, but only the first of these ($x = 1$) seems to be based on experimental evidence.

The main object of our work, which will be described in Part II, is to study the equilibrium between the various possible complexes by measuring the distribution of the substance between ether and water. For this purpose, it is essential to know the molecular complexity of the ferric thiocyanate in ethereal solution, and, as preliminary distribution experiments indicated that the thiocyanate was monomeric, a special investigation of the molecular weight in ether, alcohol, and benzene was undertaken. Our results being in direct conflict with those of Schlesinger and Van Valkenburgh, they are reported in detail.

Experimental.

Preparation of Solutions.—Repeated attempts were made to prepare pure crystalline ferric thiocyanate by Schlesinger and Van Valkenburgh's method, *i.e.*, slow evaporation of a solution made from barium thiocyanate and ferric sulphate, or from thiocyanic acid and ferric hydroxide. In no case was a pure product obtained. The only analysis which Schlesinger and Van Valkenburgh give is for total iron (= 24·49%). Gravimetric determinations as Fe_2O_3 on three of our samples gave 21·1, 22·25, and 24·1%, which approach this value. Parallel determinations of thiocyanate (by addition of excess of silver nitrate and back-titration with potassium thiocyanate gave only 5·0, 4·6, and 4·95%, respectively [Calc. for $Fe(CNS)_3$: CNS, 75·8%], and titrations with titanous sulphate and with permanganate showed that nearly all the iron was in the ferrous condition. A typical analysis of three crops of crystals from the same preparation is given below:

	CNS, %.	Fe(III), %.	Fe(II), %.
1st crop (large crystals)	10·1	2·25	—
2nd crop	16·5	2·7	—
3rd crop (small crystals)	29·3	2·6	23·6
Theory (anhydrous)	75·8	24·2	0·0

An insoluble residue which seemed to contain sulphur or polysulphides was always present. It is evident that internal oxidation–reduction was taking place. The evaporation was carried out in the dark and extended over several weeks, as recommended by Schlesinger and Van Valkenburgh.

Evaporation of the ethereal extract also did not prove satisfactory, as difficulty was experienced in drying the extract. Large quantities of sodium sulphate always decolorised the extract, and phosphoric oxide and metallic sodium also decomposed the solute. On addition of the ethereal extract to a large amount of benzene, water droplets separated and could be removed by filtration. On removal of the ether by distillation under reduced pressure, a solid separated which had the composition: CNS^- 23·6; Fe^{3+} 5·5; Fe^{3+} 19·0%. As molecular-weight determinations on preparations of such variable and uncertain composition, which were not completely soluble, would have had no significance, attempts to prepare the crystalline solid were abandoned, and solutions were prepared as follows.

(1) An aqueous solution of potassium thiocyanate, ferric sulphate, and sulphuric acid was extracted with AnalaR ether, and the wet extract used directly in the ebulliometer, its composition being determined by analysis. The extract was found to contain thiocyanic acid in considerable quantity, but to be free from sulphate. (2) An alcoholic solution of ferric sulphate was prepared indirectly by shaking a solution of ferric chloride in alcohol for some hours with solid silver sulphate. The solution contained exactly equivalent amounts of Fe^{3+} and SO_4^{2+}. This solution was then shaken for 4 hours with the exact equivalent of barium thiocyanate, and the gelatinous precipitate which formed was separated in the centrifuge. The solution again contained free thiocyanic acid, but no sulphate and only a trace of barium could be detected. (3) It was not found possible to prepare solutions in benzene at all. Benzene did not extract ferric thiocyanate from aqueous solutions of any composition tried, and when ethereal extracts were added to benzene and the ether was removed by vacuum distillation, a solid was thrown out of solution and an almost colourless filtrate was obtained. It is concluded that ferric thiocyanate is insoluble in pure benzene, though it forms a purple solution if small amounts of ether are present.

Method.—The apparatus used was Swietoslawski's differential ebulliometer ("Ebulliometry," Chem. Pub. Co., N.Y., 1945, Fig. 7), but arranged for electrical heating, a small platinum coil immersed directly in the liquid being in series with external windings. In this method, the boiling liquid is pumped over

one thermometer, while the vapour condenses on a second; the difference in the reading of the two thermometers gives the elevation and is independent of fluctuations in atmospheric pressure. When mixed solvents are used (*e.g.*, moist ether) a certain amount of fractionation is bound to occur between the two thermometers, and this was found to give rise, in the case of ether saturated with water, to a difference of 0·023°. In the experiments quoted, the Beckmann thermometers were calibrated in the apparatus, the solvent being used in the same condition as it was to be used in the final experiment, and it was assumed that the degree of fractionation occurring in the two experiments would be nearly the same.

Results.—The thermodynamic ebullioscopic constants for dry ether is 2·24, but moisture will lower this. Values for the constant given in I.C.T. for salicylic acid and for thiocyanic acid, and those calculated from our own experiments, are shown in the following table. Values marked * were made with

Salicylic acid.

Concn. (moles/1000 g.)	0·0767	0·1	0·2	0·237	0·287	0·287	0·3	0·441
K (I.C.T.)	—	2·16	2·18	—	—	—	2·22	—
K (obs.)	$2·06_5$ *	—	—	2·16	2·03 *	2·12	—	2·20

Thiocyanic acid.

Concn. (moles/1000 g.)	0·1	0·2	$0·3_5$	0·5
K (I.C.T.)	—	1·917	—	1·926
K (obs.)	2·075 *	—	2·08 *	—

ether saturated with water. These results served to check the apparatus, and showed that thiocyanic acid has its normal molecular weight in this solvent. A value of 2·06 was chosen for the ebullioscopic constant of moist ether.

The following are the results of two experiments. In the calculations, the elevation due to the thiocyanic acid was worked out and subtracted from the observed elevation. The difference is assumed to be due to the ferric thiocyanate whose molecular weight is being determined. The theoretical molecular weight for single molecules is 230.

$Fe(CNS)_3$, g./1000 g.	HCNS, g./1000 g.	Total elevation.	*M.*	$Fe(CNS)_3$, g./1000 g.	HCNS, g./1000 g.	Total elevation.	*M.*
7·866	1·04	0·112°	214	35·75	7·06	0·569°	228

The value chosen for the ebullioscopic constant of alcohol was 1·14, this being the mean of three determinations with benzoic acid in our apparatus and four from I.C.T. (maximum deviation, 3%). The results of two experiments are as follows:

$Fe(CNS)_3$, g./1000 g.	HCNS, g./1000 g.	Total elevation.	*M.*	$Fe(CNS)_3$, g./1000 g.	HCNS, g./1000 g.	Total elevation.	*M.*
22·1	1·244	0·144°	210	36·7	0·466	0·221°	197

[*Added, November 10th*, 1950.] After this paper had been submitted, Meyer, Metzler, and Swift (*J. Amer. Chem. Soc.*, 1950, **72**, 3765, 3772, 2776) showed that ferric chloride, which it might have been thought would behave in a similar manner to ferric thiocyanate, shows considerable complexity in ethereal solutions. Not only does it associate with hydrochloric acid to give the compound $HFeCl_4$, but in concentrations greater than 0·001M. it polymerises. It was therefore thought advisable to obtain independent confirmation of the monomeric character of the thiocyanate solutions.

It will be shown in Part II that if the thiocyanate concentration is kept constant (and in excess), the proportion of $Fe(CNS)_3$ to other complexes in the aqueous solution is also constant. Such solutions can therefore be considered as consisting of single molecules of the thiocyanate. If they are extracted with ether, then a constant partition coefficient will indicate that the molecules in ether are also monomeric. In an experiment at room temperature, 40 ml. of ether, previously saturated with water, were shaken with 40 ml. of aqueous solutions of composition NH_4CNS, 0·45M., $HClO_4$, 0·675N., $Fe(ClO_4)_3$, *x*M. The results are given below:

x	0·025	0·0083	0·001	0·0005	0·00025
Fe in ether/Fe in water	8·9	8·45	9·1	8·45	7·8

The concentration of iron in the ethereal layer was not very different from *x*. That of the thiocyanate in the aqueous layer was reduced to 0·21M. by extraction of thiocyanic acid. These figures may be compared with those given by Meyers *et al.* (*loc. cit.*), who report that, over the same range, the coefficient for ferric chloride varies from 1·070 to 0·317.

Discussion.—It will be seen from the tables above that there is no simple stoicheiometric relationship between the iron and the acid in ethereal and in alcoholic solutions (such as is found with ferric chloride). Thiocyanic acid is quite strongly extracted from its aqueous solution by ether, and the presence of iron does not noticeably increase the extraction ratio. These facts, together with the additive nature of the ebullioscopic elevation, show that the compound $HFe(CNS)_4$ is not formed at the concentrations studied. The slightly low value of the molecular weight found ebullioscopically is probably due to slight decomposition, the solutions being rather unstable. Conductivity measurements show that ferric thiocyanate in moist ether is not ionised, the very small conductivity being attributable to thiocyanic acid. It is therefore

concluded that ferric thiocyanate exists in solution in ether, alcohol, and similar solvents in the form of single molecules only. The results of Schlesinger and Van Valkenburgh's ebullioscopic experiments can be explained if it is assumed that they were misled by an analysis for total iron into believing that a solid product, similar to that obtained by us, was in fact a pure substance. We are at a loss, however, to explain their results in benzene, for in our experience ferric thiocyanate is insoluble in this solvent.

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UNITED COLLEGE, ST. ANDREWS. [*Received, July 31st,* 1950.]

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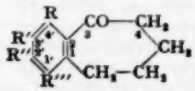
291. *Purpurogallin. Part V. Some Improvements in Synthetical Methods.*

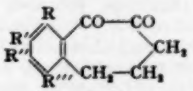
By DAVID CAUNT, WILFRID D. CROW, and ROBERT D. HAWORTH.

Improved methods for the conversion of benzo*cyclo*hepten-3-ones of type (I) into benzotropolones of type (III) have been sought. It has been found advantageous to condense compounds of type (I) with ethyl formate and to prepare diones of type (II) by ozonisation of the resulting hydroxymethylene derivatives (V) or their methyl ethers; the dehydrogenation of the diones (II) to benzotropolones of type (III) has been examined under a variety of conditions. As a result of these experiments the yields obtained in the preparation of 4-hydroxy-2′ : 3′-dimethoxybenzo*cyclo*heptatrien-3-one (III; R = R‴ = H, R′ = R″ = OMe) and purpurogallin dimethyl ether (III; R = R′ = R″ = OMe, R‴ = H) have been increased approximately fivefold, and the new methods have also been applied to the synthesis of 4-hydroxy-1′ : 2′ : 3′-trimethoxybenzo*cyclo*heptatrien-3-one (III; R = H, R′ = R″ = R‴ = OMe).

Similar improvements are also realised by the new methods of Barltrop, Johnson, and Meakins (*J.*, 1951, 181).

IN Part III (*J.*, 1950, 1631) 4-hydroxy-2′ : 3′-dimethoxybenzo*cyclo*heptatrien-3-one (III; R = R‴ = H, R′ = R″ = OMe) and purpurogallin 2′ : 3′-dimethyl ether (III; R = OH, R′ = R″ = OMe, R‴ = H) * were synthesised by oxidation of 2′ : 3′-dimethoxy- (I; R = R‴ = H, R′ = R″ = OMe) and 2′ : 3′ : 4′-trimethoxy-benzo*cyclo*hepten-3-one (I; R = R′ = R″ = OMe, R‴ = H) respectively with selenium dioxide to the corresponding 3 : 4-diones (II), followed by dehydrogenation with palladium–charcoal. The yields in these two stages were approximately 50% and 8% respectively. New and improved methods described in this communication have improved the overall yields of these two benzotropolones (III; R = R‴ = H, R′ = R″ = OMe) and (III; R = OH, R′ = R″ = OMe, R‴ = H) from 4% to nearly 20%. In addition to this the methods have been successfully applied to the synthesis of 4-hydroxy-1′ : 2′ : 3′-trimethoxybenzo*cyclo*heptatrien-3-one (III; R = H, R′ = R″ = R‴ = OMe), an isomer of purpurogallin trimethyl ether.


(I.)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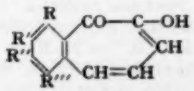
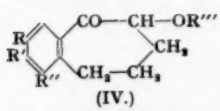
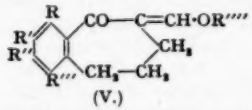

(III.)

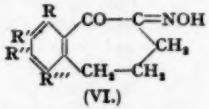
The earlier methods described in Part III (*loc. cit.*) suffered from one obvious defect in that the 3 : 4-diones (II) so obtained were difficult to purify from traces of selenium, and it seemed probable that these would poison the catalyst used for the subsequent dehydrogenation, as indeed proved to be the case. Some improvement in purity was effected by shaking an ethereal solution of the dione with aqueous sodium hydrogen sulphide; this removed the selenium but, as small amounts of dione were also removed and traces of sulphur were introduced, other methods of synthesis were sought which avoided the use of selenium dioxide completely.

* In this and the following papers, as in previous Parts of the series, formulation of purpurogallin derivatives as (III) does not exclude their existence in the form in which the keto- and hydroxy-groups of the *cyclo*heptatriene ring are interchanged.

It was shown that 1′ : 2′ : 3′-trimethoxybenzo*cyclo*hepten-3-one (I; R = H, R′ = R″ = R‴ = OMe), prepared by an improved method described on p. 1316, was converted into 4-acetoxy-1′ : 2′ : 3′-trimethoxybenzo*cyclo*hepten-3-one (IV; R = R′ = R″ = OMe, R‴ = Ac) by oxidation with lead tetra-acetate in warm acetic acid solution. This acetoxy-compound was hydrolysed by potassium carbonate solution to an oily ketol (IV; R = R′ = R″ = OMe, R‴ = H), but attempted dehydrogenation of the acetoxy-compound or the ketol gave unsatisfactory results. The ketol (IV; R = R′ = OMe, R″ = R‴ = H) prepared similarly from 2′ : 3′-dimethoxybenzo*cyclo*hepten-3-one (I; R = R‴ = H, R′ = R″ = OMe) was an oil, giving a *p*-nitrobenzoate, m. p. 183°, identical with that obtained previously (Part III, *loc. cit.*) by the action of nitrous acid on 4-amino-2′ : 3′-dimethoxybenzo*cyclo*hepten-3-one. The crude ketol (IV; R = R′ = OMe, R″ = R‴ = H) was dehydrogenated with palladium–charcoal in boiling trichlorobenzene to 4-hydroxy-2′ : 3′-dimethoxybenzo*cyclo*heptatrien-3-one (III; R = R‴ = H, R′ = R″ = OMe), m. p. 147° (Part III, *loc. cit.*), but in view of the minute yield (0·5%) this approach was abandoned. Preliminary attempts to convert the ketol (IV; R = R′ = R″ = OMe, R‴ = H) into the corresponding 3 : 4-dione (II; R = H, R′ = R″ = R‴ = OMe) by Oppenauer oxidation (*cyclo*hexanone, aluminium *iso*propoxide) were also discouraging.


(IV.)


(V.)


(VI.)

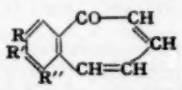
It was shown in Part III (*loc. cit.*) that 4-hydroxymethylene-2′ : 3′-dimethoxybenzo*cyclo*hepten-3-one (V; R = R‴ = R⁗ = H, R′ = R″ = OMe) was readily obtained by condensation of the requisite ketone (I; R = R‴ = H, R′ = R″ = OMe) with ethyl formate under the influence of sodium methoxide. Repetition of this experiment has shown that high yields (85—90%) are readily obtainable, and equally good results have been obtained for the conversion of 1′ : 2′ : 3′- (I; R = H, R′ = R″ = R‴ = OMe) and 2′ : 3′ : 4′-trimethoxybenzo*cyclo*hepten-3-one (I; R = R′ = R″ = OMe, R‴ = H) into the corresponding 4-hydroxymethylene compounds. Treatment with ethereal diazomethane or methanolic hydrogen chloride converted the 4-hydroxymethylene derivatives quantitatively into the corresponding methyl ethers (V; R⁗ = Me); the 2′ : 3′-dimethoxy- and the 1′ : 2′ : 3′-trimethoxy-compound have so far only been obtained as oils. The 4-hydroxymethylene or 4-methoxymethylene derivatives were ozonised in ethyl acetate at −70°, giving 2′ : 3′-dimethoxy-, 1′ : 2′ : 3′-trimethoxy-, and 2′ : 3′ : 4′-trimethoxy-benzo*cyclo*heptene-3 : 4-diones (II) in 100, 87, and 90% yields respectively; the diones were identified by 2 : 4-dinitrophenylhydrazones. Use of excess of ozone resulted in ring fission, and the corresponding γ-*o*-carboxyphenylbutyric acid was isolated in each case.

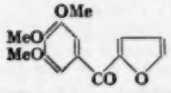
An alternative approach to the 3 : 4-diones (II) *via* the 4-oximino-derivatives (VI) was investigated previously (Part III, *loc. cit.*). The 4-oximino-derivative (VI; R = R‴ = H, R′ = R″ = OMe), obtained in 50% yield by the action of *iso*amyl nitrite on the corresponding ketone (I) in the presence of methanolic hydrogen chloride, was hydrolysed with pyruvic acid and strong hydrochloric acid, but gave only a 30% yield of the 3 : 4-dione as an oil, together with much resinous material. Recently Barltrop, Johnson, and Meakins (*J.*, 1951, 181) have modified and improved the preparation of 2′ : 3′-dimethoxy-4-oximinobenzo*cyclo*hepten-3-one (VI; R = R‴ = H, R′ = R″ = OMe), and shown that hydrolysis is effected in high yield by formaldehyde and dilute hydrochloric acid, giving the 3 : 4-dione (II; R = R‴ = H, R′ = R″ = OMe) as a crystalline solid. Clearly our earlier conditions were too drastic, and resulted in further condensation of the dione to resinous material. We have confirmed the results of Barltrop, Johnson, and Meakins and obtained 2′ : 3′-dimethoxybenzo*cyclo*heptene-3 : 4-dione (II; R = R‴ = H, R′ = R″ = OMe), m. p. 104°, in overall yield of 68%. Extension of this method to the trimethoxy-series has resulted in the formation of 1′ : 2′ : 3′- and 2′ : 3′ : 4′-trimethoxybenzo*cyclo*heptene-3 : 4-dione (II) in overall yields of 75%. These diones do not crystallise and have been characterised as their 2 : 4-dinitrophenylhydrazones. In agreement with previous experiments in the dimethoxy-series it was found that 1′ : 2′ : 3′-trimethoxybenz*cyclo*heptene-3 : 4-dione (II; R = H, R′ = R″ = R‴ = OMe) gave only a poor yield (approximately 10%) of 4-hydroxy-1′ : 2′ : 3′-trimethoxybenzo*cyclo*heptatrien-3-one (III; R = H, R′ = R″ = R‴ = OMe) when dehydrogenated with palladium–charcoal in the usual way. This yield was doubled when the dione employed for dehydrogenation was prepared by

ozonolysis of the 4-hydroxymethylene derivative or by hydrolysis of the 4-oximino-derivative. Similar results were obtained with the other diones (II; R = R‴ = H, R′ = R″ = OMe) and (II; R = R′ = R″ = OMe, R‴ = H). A quantitative study of this dehydrogenation reaction has shown that the volume of hydrogen evolved bears little relation to the amount of product formed, although the ratio of the two is approximately constant for a given catalyst. The yields could not be increased by replacing trichlorobenzene by other solvents, or by addition of maleic anhydride to the system, and chloranil and *p*-benzoquinone were found to be ineffective as dehydrogenating agents.

The synthesis of purpurogallin 2′ : 3′-dimethyl ether (Part III, *loc. cit.*) was repeated, extreme precautions being taken against demethylation during the isolation process. The failure to obtain the unknown 2′ : 3′ : 4′-trimethyl ether proved conclusively that demethylation was effected during the dehydrogenation. In this connection it is noteworthy that dehydrogenation of 1′ : 2′ : 3′-trimethoxybenzo*cyclo*hepten-3-one (I; R = H, R′ = R″ = R‴ = OMe) gave in low yield a phenol, m. p. 130—131°, analysing as a dimethyl ether of 1′ : 2′ : 3′-trihydroxybenzo*cyclo*heptatrien-3-one (VII; R = R′ = R″ = OH). The demethylation being assumed to have resulted from the usual activation at positions *ortho* and *para* to a *meta*-directing substituent, this phenol would be expected to be 2′-hydroxy-1′ : 3′-dimethoxybenzo*cyclo*heptatrien-3-one (VII; R = R″ = OMe, R′ = OH). The formation of purpurogallin dimethyl ether may be explained on a similar basis.

(VII.)





(VIII.)

During the course of the experiments outlined above it was decided to attempt the synthesis of 4-hydroxy-1′ : 2′ : 3′-trimethoxybenzo*cyclo*heptatrien-3-one (III; R = H, R′ = R″ = R‴ = OMe) by direct rearrangement of 2-furyl 3′ : 4′ : 5′-trimethoxyphenyl ketone (VIII). This compound was prepared by the action of 3 : 4 : 5-trimethoxybenzoyl chloride on furan in nitrobenzene, aluminium chloride being used as catalyst. It was obtained as a nearly colourless solid, m. p. 108—109°, giving a red 2 : 4-dinitrophenylhydrazone, m. p. 201—202°. Rearrangement could not be effected by 20% hydrochloric acid at 150°, the products giving unchanged ketone on remethylation. The use of 46% hydrobromic acid resulted in extensive resinification, and this line of attack was abandoned.

Experimental.

*2′ : 3′-Dimethoxy-4-methoxymethylenebenzo*cyclo*hepten-3-one* (V; R = R‴ = H, R′ = R″ = OMe, R⁗ = Me).—4-Hydroxymethylene-2′ : 3′-dimethoxybenzo*cyclo*hepten-3-one (Part III, *loc. cit.*) (10·0 g.) was refluxed for 30 minutes with methanol (100 c.c.) containing a little hydrogen chloride. Removal of the solvent gave the *methyl ether* (10·4 g.) which separated from methanol in colourless plates, m. p. 117° (Found: C, 68·3; H, 7·1. $C_{15}H_{18}O_4$ requires C, 68·6; H, 6·9%).

*2′ : 3′-Dimethoxybenzo*cyclo*heptene-3 : 4-dione* (II; R = R‴ = H, R′ = R″ = OMe).—The methyl ether, described above (10·0 g.), in ethyl acetate (50 c.c.) was cooled to −70° and allowed to react with one molecular equivalent of ozone. The resultant solution was hydrogenated over palladium–charcoal with cooling until one mol. of hydrogen was absorbed. Filtration and removal of the solvent under reduced pressure yielded the dione (8·9 g.) as a yellow oil. Crystallisation first from water and then from *cyclo*hexane gave yellow prisms, m. p. 104° (Found: C, 66·4; H, 5·9. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%). The *disemicarbazone* crystallised from alcohol in colourless plates, m. p. 248° (Found: C, 50·8; H, 5·5. $C_{15}H_{22}O_2N_6$ requires C, 50·8; H, 5·8%).

When excess of ozone was used a small amount of *γ-(2-carboxy-4 : 5-dimethoxyphenyl)butyric acid* was isolated by extraction with sodium hydrogen carbonate solution and separated from alcohol as colourless prisms, m. p. 165° (Found: C, 58·4; H, 6·2. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%). Dehydrogenation of the 3 : 4-dione in the usual way (Part III, *loc. cit.*) gave 4-hydroxy-2′ : 3′-dimethoxybenzo*cyclo*heptatrien-3-one (III; R = R‴ = H, R′ = R″ = OMe) in 22% yield.

*4-Hydroxy-2′ : 3′-dimethoxybenzo*cyclo*hepten-3-one* (IV; R = R′ = OMe, R″ = R‴ = H).—2′ : 3′-Dimethoxybenzo*cyclo*hepten-3-one (5·0 g.) was heated on the water-bath for 2 hours with lead tetra-acetate (8·0 g.) in dry acetic acid (25 c.c.), and the solution was diluted with water (250 c.c.) and extracted with ether. After being washed (to remove acetic acid), the extracts were concentrated, giving a light yellow oil (5·2 g.) which could not be obtained crystalline. After distillation the oil (b. p. 165—185°/0·01 mm.), which did not solidify, was hydrolysed with aqueous-methanolic potassium carbonate on the water-bath for 2 hours. The product, a dark brown oil (4·5 g.), did not crystallise and decomposed on attempted distillation. On storage unchanged 2′ : 3′-dimethoxybenzo*cyclo*hepten-3-one (2·1 g.) crystallised and the residual ketol gave, in the usual way, a *p*-nitrobenzoate, which separated from *cyclo*hexane in colourless prisms, m. p. 183°, identical with the product obtained from 4-oximino-2′ : 3′-dimethoxybenzo*cyclo*hepten-3-one (Part III, *loc. cit.*).

The ketol (3·0 g.; crude) was dehydrogenated in the usual way giving 4-hydroxy-2′ : 3′-dimethoxybenzocycloheptatrien-3-one (0·016 g.) which crystallised from *cyclo*hexane in deep yellow prisms, m. p. 145—146°.

1′ : 2′ : 3′-*Trimethoxybenzo*cyclo*hepten*-3-*one* (I; R = H, R′ = R″ = R‴ = OMe).—δ-(2 : 3 : 4-Trimethoxyphenyl)valeric acid (13·4 g.) (Part I, *J.*, 1948, 1051) in dry benzene (150 c.c.) was treated for 2 hours at 0° with phosphorus pentachloride (11·0 g.) and pyridine (0·1 c.c.), and the reaction completed by warming on the water-bath for 10 minutes. The solution was again cooled to 0°, added to an ice-cold solution of stannic chloride (redistilled; 8·5 c.c.) in dry benzene (2 l.), kept for 15 hours at 0°, and hydrolysed by addition of ice (250 g.) and concentrated hydrochloric acid (250 c.c.). The benzene layer was washed successively with water, 20% sodium hydroxide solution (500 c.c.), and water, dried, and freed from solvent. Distillation of the oily residue gave the ketone (8·8 g.) as a colourless oil, b. p. 152—155°/0·3 mm.* Acidification of the alkaline extracts afforded a little unchanged acid (3·0 g.). The ketone gave a 2 : 4-*dinitrophenylhydrazone*, existing in two interchangeable forms: red prisms (from acetic acid), m. p. 181—182° (Part I, *loc. cit.*), and yellow needles (from alcohol), m. p. 181—182° (Found: C, 56·0; H, 5·2; N, 12·9. $C_{29}H_{32}O_7N_4$ requires C, 55·8; H, 5·1; N, 13·0%), and a *semicarbazone*, which crystallised from aqueous methanol in colourless needles, m. p. 197—198° (Found: C, 58·5; H, 6·9; N, 13·9. $C_{16}H_{21}O_4N_3$ requires C, 58·6; H, 6·9; N, 13·7%).

Dehydrogenation of 1′ : 2′ : 3′-*Trimethoxybenzo*cyclo*hepten*-3-*one* (I; R = H, R′ = R″ = R‴ = OMe).—The ketone described above (5·0 g.) was refluxed for 15 hours with 10% palladium–charcoal (5·0 g.) in 1 : 2 : 4-trichlorobenzene (20 c.c.) with a current of nitrogen. After dilution with ether (10 volumes) and filtration the solution was washed with sodium hydrogen carbonate solution (which removed traces of tarry and acidic material), then repeatedly with sodium hydroxide. Acidification of the sodium hydroxide extracts afforded a small quantity (0·06 g.) of a colourless *phenol* (possibly VII; R′ = R″ = OMe, R′ = H), which separated from light petroleum (b. p. 40—60°) in needles, m. p. 130—131° (Found: C, 65·4; H, 6·7; OMe, 26·2. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·0; OMe, 26·8%), which gave a slow positive test with Brady's reagent.

The neutral residues of the dehydrogenation were treated with Girard reagent T in the usual way, but only unchanged 1′ : 2′ : 3′-trimethoxybenzo*cyclo*hepten-3-one (2·0 g.) was recovered.

4-*Hydroxymethylene*-1′ : 2′ : 3′-*trimethoxybenzo*cyclo*hepten*-3-*one* (V; R = R‴ = H, R′ = R″ = R‴ = OMe) was prepared in 85% yield from 1′ : 2′ : 3′-trimethoxybenzo*cyclo*hepten-3-one (I; R = H, R′ = R″ = R‴ = OMe) by the method described in Part III (*loc. cit.*). It crystallised from aqueous methanol in colourless needles, m. p. 71·5—72·5° (Found: C, 64·5; H, 6·3. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·5%), and gave a violet-red ferric colour. The 2 : 4-*dinitrophenylhydrazone* crystallised in dark red plates (from acetic acid), m. p. 176—177° (Found: C, 54·6; H, 4·7; N, 12·5. $C_{21}H_{22}O_8N_4$ requires C, 55·0; H, 4·8; N, 12·2%).

Methylation of the hydroxymethylene compound (2·0 g.) with excess of ethereal diazomethane gave the *methyl ether* (2·0 g.) which gave no ferric colour and crystallised from aqueous methanol in colourless needles, m. p. 107—108° (Found: C, 66·0; H, 6·7. $C_{16}H_{20}O_5$ requires C, 65·7; H, 6·9%).

1′ : 2′ : 3′-*Trimethoxy*-4-*oximinobenzo*cyclo*hepten*-3-*one* (VI; R = H; R′ = R″ = R‴ = OMe) was prepared in 85% yield as described by Barltrop, Johnson, and Meakins (*loc. cit.*) by the action of *iso*amyl nitrite in ethereal hydrogen chloride on the ketone (I; R = H, R′ = R″ = R‴ = OMe) at −70°. The hydrochloride of the product was precipitated by the addition of light petroleum (b. p. 40—60°). The resultant oil was converted into the base with sodium hydrogen carbonate solution, and crystallised from aqueous methanol in pale yellow hydrated prisms, m. p. 132—133° (Found: C, 56·4; H, 6·4; N, 4·8. $C_{14}H_{17}O_5N,H_2O$ requires C, 56·6; H, 6·4; N, 4·7%), or from benzene–light petroleum (b. p. 40—60°) in pale yellow needles, m. p. 135—136° (Found: C, 60·1; H, 6·1. $C_{14}H_{17}O_5N$ requires C, 60·1; H, 6·1%).

1′ : 2′ : 3′-*Trimethoxybenzo*cyclo*heptene*-3 : 4-*dione* (II; R = H, R′ = R″ = R‴ = OMe).—(*a*) The ketone (I; R = H, R′ = R″ = R‴ = OMe) (10·0 g.) was refluxed for 4 hours in *n*-butyl alcohol (75 c.c.) with selenium dioxide (4·44 g.), diluted with ether (2 volumes), and filtered, and all solvents were then removed under reduced pressure. Distillation of the residual oil gave a yellow oil (8·1 g.), b. p. 140—170°/0·2 mm., which was dissolved in ether, and passed through a column of alumina (5 × 0·5 cm.). Continued elution with ether (total, 500 c.c.) gave, after concentration, an oil, which on distillation yielded unchanged ketone (I; R = H, R′ = R″ = R‴ = OMe) (0·65 g.) and the 3 : 4-dione as a viscous yellow oil (7·0 g.), b. p. 166—170°/0·2 mm., which could not be obtained crystalline. The dione dissolved in aqueous sodium hydroxide to give a yellow solution, and gave a 2 : 4-*dinitrophenylhydrazone*, crystallising from acetic acid in orange needles, m. p. 177—178° (Found: C, 54·3; H, 4·6; N, 12·5. $C_{20}H_{20}O_8N_4$ requires C, 54·1; H, 4·5; N, 12·6%).

(*b*) 4-Hydroxymethylene-1′ : 2′ : 3′-trimethoxybenzo*cyclo*hepten-3-one (3·0 g.) was submitted to ozonolysis as described for the methyl ether of the 2′ : 3′-dimethoxy-analogue (p. 1315). Extraction of the dione solution with sodium hydrogen carbonate solution gave a little γ-(6-carboxy-2 : 3 : 4-trimethoxyphenyl)butyric acid, m. p. 140—141° [in Part I (*loc. cit.*) this was reported as m. p. 132°], identical with an authentic specimen. Evaporation of the organic layer yielded the 3 : 4-dione (2·35 g.) as a yellow oil, b. p. 166—170°/0·2 mm.

(*c*) The 3 : 4-dione was also prepared in 94% yield by hydrolysis of 1′ : 2′ : 3′-trimethoxy-4-oximino-benzo*cyclo*hepten-3-one as described for the 2′ : 3′-dimethoxy-analogue.

4-*Acetoxy*-1′ : 2′ : 3′-*trimethoxybenzo*cyclo*hepten*-3-*one* (IV; R = R′ = R″ = OMe, R‴ = Ac) prepared in 80% yield as described for the dimethoxy-analogue (p. 1315) was obtained as colourless needles

* The b. p. of this compound was erroneously recorded in Part I as 170°/0·3 mm.

(from *cyclo*hexane), m. p. 97—98° (Found: C, 62·2; H, 6·5. $C_{14}H_{20}O_6$ requires C, 62·3; H, 6·5%). Hydrolysis by the method described previously gave a yellow oily ketol which could not be satisfactorily distilled and did not crystallise. This compound (2·0 g.) was refluxed for 6 hours with *cyclo*hexanone (10 c.c.), toluene (100 c.c.), and aluminium *iso*propoxide (1·4 g.), and the mixture hydrolysed with hydrochloric acid (250 c.c.; 10%). Evaporation of the organic layer gave a deep red oil (1·75 g.) which on distillation gave a viscous orange oil (1·2 g.), b. p. 195—210°/0·1 mm. Treatment with Brady's reagent in large excess gave a small amount (0·8 g.) of a product, crystallising from acetic acid in orange plates, m. p. 257—259° (Found: C, 50·3; H, 4·2; N, 17·8. $C_{26}H_{32}O_{11}N_8$ requires C, 50·0; H, 3·9; N, 17·9%). The same product, probably the *bis*-2:4-*dinitrophenylhydrazone* of the dione, was also obtained by prolonged action of Brady's reagent on 1′:2′:3′-trimethoxy-4-oximinobenzo*cyclo*hepten-3-one. Dehydrogenation of the ketol acetate in the usual way gave a small amount of unidentified phenol crystallising from *cyclo*hexane in colourless needles, m. p. 152—153° (Found: C, 63·4; H, 5·6%).

4-*Hydroxy*-1′:2′:3′-*trimethoxybenzo*cyclo*heptatrien*-3-*one* (III; R = H, R′ = R″ = R‴ = OMe).—1′:2′:3′-Trimethoxybenzo*cyclo*heptene-3:4-dione [0·5 g.; obtained by method (*b*) above] was refluxed for 10 hours with 10% palladium–charcoal (0·5 g.) (*Org. Synth.*, **26**, 78) in 1:2:4-trichlorobenzene (5 c.c.) in a current of carbon dioxide. The hydrogen evolved was measured over 40% potassium hydroxide solution. The mixture was diluted with ether and filtered, and the catalyst extracted twice with boiling 10% sodium hydroxide solution. The product recovered by acidification was taken up in ether and mixed with the original organic solvents.

The organic solvents were extracted with sodium hydrogen carbonate solution, then twice with 10% sodium hydroxide solution, and finally washed with water. Acidification of the bicarbonate extract gave an acid (*ca.* 0·04 g.) which was not further investigated. Similar treatment of the combined sodium hydroxide extracts and washings gave, after isolation with ether and crystallisation from *cyclo*hexane, 4-*hydroxy*-1′:2′:3′-*trimethoxybenzo*cyclo*heptatrien*-3-*one* (0·105 g.) which separated in yellow needles, m. p. 91—92° (Found: C, 63·7; H, 5·2. $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·4%). This was soluble in alkali to give a yellow solution, gave a crimson ferric colour, extractable by chloroform, and a crimson coupling product with diazotised *p*-toluidine.

The ultra-violet spectrum was measured in M/20,000 solution in methanol. The values obtained for $\lambda_{max.}$, in mμ., are followed in parentheses by the corresponding values for $\log_{10} \varepsilon$: 208 (4·20), 280 (4·49), 297·5 (4·25), 350 (3·81), 405 (3·74). Points of inflexion were observed at 273 (4·43) and 450 (2·68).

4-*Hydroxymethylene*-2′:3′:4′-*trimethoxybenzo*cyclo*hepten*-3-*one* (V; R = R′ = R″ = OMe, R‴ = R⁗ = H), prepared from 2′:3′:4′-trimethoxybenzo*cyclo*hepten-3-one (Part III, *loc. cit.*) in 88% yield by the method described previously (p. 1316), crystallised in colourless needles from aqueous methanol, m. p. 112—113° (Found: C, 65·6; H, 6·4. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·5%), and gave a violet-red ferric colour. The 2:4-*dinitrophenylhydrazone* crystallised from acetic acid in dark red needles, m. p. 204—205° (Found: C, 54·9; H, 4·6; N, 12·0. $C_{21}H_{22}O_8N_4$ requires C, 55·0; H, 4·8; N, 12·2%).

Attempted methylation of the hydroxymethylene compound with sodium methoxide and methyl iodide resulted in the formation of 2′:3′:4′-*trimethoxy*-4-*methylbenzo*cyclo*hepten*-3-*one* which separated from aqueous methanol in needles, m. p. 87—88° (Found: C, 68·2; H, 7·4. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%). The use of excess of ethereal diazomethane gave 2′:3′:4′-*trimethoxy*-4-*methoxymethylenebenzo*cyclo*hepten*-3-*one* (V; R = R′ = R″ = OMe, R‴ = H, R⁗ = Me) in 95% yield as a colourless oil, b. p. 158—160°/0·1 mm., which could not be obtained crystalline. It gave no ferric colour, but formed a 2:4-*dinitrophenylhydrazone*, separating from aqueous acetic acid in dark red needles, m. p. 189—190° (Found: C, 56·1; H, 5·2; N, 11·8. $C_{22}H_{24}O_8N_4$ requires C, 55·9; H, 5·1; N, 11·9%).

2′:3′:4′-*Trimethoxy*-4-*oximinobenzo*cyclo*hepten*-3-*one* (IV; R = R′ = R″ = OMe, R‴ = H), prepared as described for the 1′:2′:3′-trimethoxy-isomer (p. 1316) (yield 85%), crystallised from benzene–ligroin in pale yellow prisms, m. p. 175—176° (Found: C, 60·0; H, 6·2; N, 5·0. $C_{14}H_{17}O_6N$ requires C, 60·1; H, 6·1; N, 5·0%).

2′:3′:4′-*Trimethoxybenzo*cyclo*heptene*-3:4-*dione* (II; R = R′ = R″ = OMe; R‴ = H).—(i) 4-Hydroxymethylene-2′:3′:4′-trimethoxybenzo*cyclo*hepten-3-one (2·0 g.) was ozonised as described for the 1′:2′:3′-trimethoxy-isomer (p. 1316). There was obtained a little γ-(2-carboxy-3:4:5-trimethoxyphenyl)butyric acid, m. p. 146—147°, identical with an authentic specimen, together with the 3:4-dione (1·62 g.) obtained as a yellow oil and identified as its 2:4-dinitrophenylhydrazone, m. p. 180—181°.

(ii) The 3:4-dione was obtained in 90% yield as a yellow oil by hydrolysis of 2′:3′:4′-trimethoxy-4-oximinobenzo*cyclo*hepten-3-one as described for the 2′:3′-dimethoxy-isomer, and identified as its 2:4-dinitrophenylhydrazone.

Dehydrogenation of 2′:3′:4′-*Trimethoxybenzo*cyclo*heptene*-3:4-*dione*.—The 3:4-dione obtained above by ozonolysis was dehydrogenated as described for the 1′:2′:3′-trimethoxy-isomer, and the alkaline extracts neutralised carefully at −10° to avoid demethylation. The solution was extracted with ether, then washed repeatedly with water, and the ether removed. Crystallisation of the residue from methanol gave, in 20% yield, orange plates, m. p. 156—157°, identical with an authentic specimen of purpurogallin dimethyl ether.

2-*Furyl* 3′:4′:5′-*Trimethoxyphenyl Ketone*.—3:4:5-Trimethoxybenzoyl chloride (11·5 g.) and furan (3·4 g.) in dry nitrobenzene (50 c.c.) were added gradually, with shaking, to a solution of anhydrous aluminium chloride (8·0 g.) in dry nitrobenzene (50 c.c.) at 0°. After 24 hours at room temperature the mixture was decomposed with ice (100 g.) and hydrochloric acid (10N.; 100 c.c.), and the nitrobenzene removed by steam-distillation. The residue was treated with methyl sulphate and sodium hydroxide solution, and the neutral fraction extracted with chloroform. The residue after evaporation of the chloroform was repeatedly extracted with boiling *cyclo*hexane, and the combined extracts were evaporated to

dryness. Recrystallisation of the product from a little ether gave the *ketone* (6·65 g.) as pale cream-coloured needles, m. p. 108—109° (Found : C, 64·2; H, 5·3. $C_{14}H_{14}O_4$ requires C, 64·1; H, 5·4%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid in fine red needles, m. p. 201—202° (Found : C, 54·2; H, 3·7; N, 13·1. $C_{20}H_{18}O_8N_4$ requires C, 54·3; H, 4·1; N, 12·7%).

On treatment of the ketone with hydrochloric acid (5N.) at 150° for 4 hours a pale yellow amorphous product was obtained. Methylation of this gave the original ketone, m. p. 108—109°. Treatment of the ketone with hydrobromic acid (46%) under reflux for 30 minutes gave a tarry red mass from which no tractable products could be isolated.

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THE UNIVERSITY, SHEFFIELD, 10. [*Received, February 10th*, 1951.]

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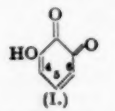
292. *Purpurogallin. Part VI. Mechanism of the Oxidation of Pyrogallol.*

By ALAN CRITCHLOW, ROBERT D. HAWORTH, and PETER L. PAUSON.

As none of the three hexahydroxydiphenyls theoretically derivable from pyrogallol is converted into purpurogallin by oxidation, the mechanism advanced by Willstätter and Heiss in 1923 for the oxidation of pyrogallol must be modified. Their suggestion that 3-hydroxy-1 : 2-benzoquinone is the first product of the oxidation sequence is accepted but, in view of the dual anionoid and cationoid reactivities of hydroxy-*o*-quinones, this primary product would be expected to yield the hypothetical *o*-diphenoquinone (III), without the intermediate formation of a hexhydroxydiphenyl. The subsequent changes may follow the benzilic acid transformation, postulated by Willstätter and Heiss and modified in Part I of this series to accommodate the purpurogallin formula (VI; R = R′ = R″ = R‴ = H), but an alternative and more attractive explanation is discussed in this communication.

The modified mechanism is consistent with the formation of a monoethyl ether (VI; R = R″ = R‴ = H, R′ = Et) of purpurogallin, by oxidation of a mixture of pyrogallol and 3-ethoxycatechol, and the structure (VI; R = R″ = R‴ = H, R′ = Et) was established by methylation and oxidation to 5-ethoxy-3 : 4-dimethoxyphthalic acid (VIII), which has been synthesised by an independent method.

PYROGALLOL is converted with remarkable ease into purpurogallin by a variety of oxidising agents in neutral or weakly acidic solutions, and Willstätter and Heiss (*Annalen*, 1923, **433**, 17) put forward an ingenious explanation of the formation of purpurogallin which they considered to be (V; R = H). On the assumption that pyrogallol was oxidised to 3-hydroxy-1 : 2-benzoquinone (I) which in its tautomeric triketo-form reacted with excess of pyrogallol to give 2 : 3 : 4 : 3′ : 4′ : 5′-hexahydroxydiphenyl (II; R = R′ = H), it was postulated that further oxidation led to the tetrahydroxy-*o*-diphenoquinone (III; R = H). This *o*-quinone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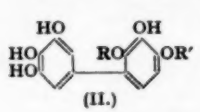
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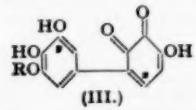
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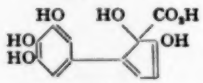
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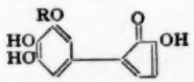
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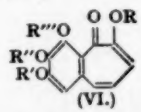

(VI.)

was believed to undergo a benzilic acid type of rearrangement to give the α-hydroxy-acid (IV) from which (V; R = H) was obtained by decarboxylation and dehydrogenation. However,

as a result of recent work, structure (V; R = H) has been disproved and the new formula (VI; R = R′ = R″ = R‴ = H) established for purpurogallin. In Part I (*J.*, 1948, 1045) it was pointed out that a modification of the Willstätter–Heiss hypothesis, in which the benzilic acid rearrangement of (III; R = H) instead of occurring at position *x*, was assumed to involve the more remotely conjugated position *y*, would be consistent with the new formula (VI; R = R′ = R″ = R‴ = H) for purpurogallin.

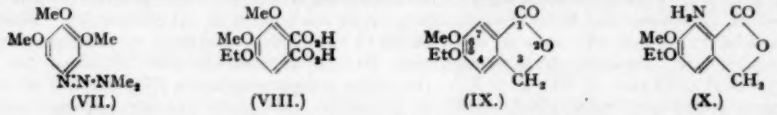
Several objections to the original, or to the modified, Willstätter–Heiss hypothesis may be raised. None of the intermediate products (II; R = R′ = H) (III; R = H), or (IV) was isolated from the reaction or proved to react as required. Of the three isomeric hexahydroxydiphenyls derivable from pyrogallol, the 2 : 3 : 4 : 2′ : 3′ : 4′-isomer was excluded because this compound, prepared by atmospheric oxidation of pyrogallol in barium hydroxide solution (Harries, *Ber.*, 1902, **35**, 2954), could not be oxidised to purpurogallin, and the 3 : 4 : 5 : 3′ : 4′ : 5-isomer (Liebermann, *Annalen*, 1873, **169**, 241) because (*a*) the oxidation of gallic acid to purpurogallin-carboxylic acid was inexplicable on this basis and (*b*) this hexahydroxydiphenyl did not yield purpurogallin on further oxidation. Consequently the 2 : 3 : 4 : 3′ : 4′ : 5′-structure (II; R = R′ = H) was the favoured intermediate diphenyl derivative, but as this compound was unknown Willstätter and Heiss were unable to verify the hypothesis experimentally. Furthermore whilst structure (II; R = R′ = H) would be expected to arise from the reaction between pyrogallol and 3-hydroxy-1 : 2-benzoquinone (I), no explanation was advanced for the preferential oxidation of (II; R = R′ = H) to the *o*-diphenoquinone (III), instead of to an isomeric *p*-diphenoquinone which could play no further part in the reaction sequence leading purpurogallin.

Attempts to condense 3 : 3-dimethyl-1-(3 : 4 : 5-trimethoxyphenyl)triazen (VII) with trimethoxybenzene by the general method of Elks and Hey (*J.*, 1943, 441) were not successful, but it has now been shown that the action of copper powder at 270° on a mixture of 4- and 5-iodotrimethoxybenzene (Erdtmann, *Proc. Roy. Soc.*, 1933, *A*, **143**, 209; Graebe and Suter, *Annalen*, 1905, **340**, 222) yields the three hexamethoxydiphenyls in approximately equal amounts. The isomers were separated by fractional crystallisation; the 2 : 3 : 4 : 2′ : 3′ : 4′- and the 3 : 4 : 5 : 3′ : 4′ : 5′-derivative were obtained from the "head" and "middle" fractions respectively, and the "tail" fraction yielded the new 2 : 3 : 4 : 3′ : 4′ : 5′-hexamethoxydiphenyl, m. p. 89°. Demethylation was effected in all three cases by boiling hydrobromic acid, but attempts to oxidise the two known hexahydroxydiphenyls or the new 2 : 3 : 4 : 3′ : 4′ : 5′-hexahydroxydiphenyl (m. p. >300°; hexa-acetate, m. p. 167°) with potassium iodate, ferricyanide, or nitrite to purpurogallin were unsuccessful. Consequently the Willstätter–Heiss theory or any alternative based on the intermediate formation of a hexahydroxydiphenyl from pyrogallol is untenable.

It will be observed that 3-hydroxy-1 : 2-benzoquinone (I) exhibits cationoid activity at position 5 (and to a less a degree at 4), and anionoid reactivity (possibly in the tautomeric triketo-form) at position 6, and consequently two molecules of this quinone would be expected to react to give the *o*-diphenoquinone (III; R = H) directly, without intermediate production of the hexahydroxydiphenyl. As the *o*-diphenoquinone (III; R = H) is unknown it is impossible to obtain direct experimental proof of its participation in the oxidation sequence, but the intermediate formation of the *o*-diphenoquinone is consistent with other evidence relating to the mechanism of formation of purpurogallin.

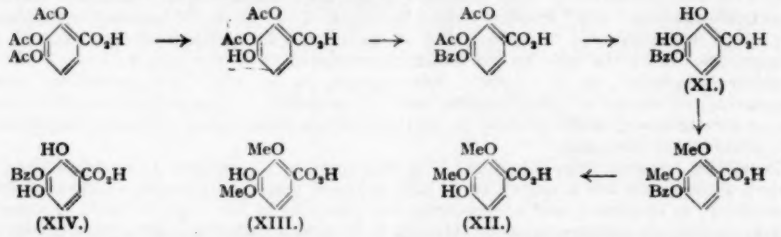
Willstätter and Heiss (*loc. cit.*) showed that neither 1 : 2-dihydroxy-3-methoxybenzene nor 3-methoxy-1 : 2-benzoquinone could be oxidised to a dimethyl ether of purpurogallin, but oxidation of either in the presence of pyrogallol gave a monomethyl ether of purpurogallin. The inactivity of 1 : 2-dihydroxy-3-methoxybenzene was associated with its inability to react in a triketo-form and consequently the reaction was assumed to occur between 3-hydroxy-1 : 2-benzoquinone and 1 : 2-dihydroxy-3-methoxybenzene to give either (II; R = H, R′ = Me) or (II; R = Me, R′ = H). It is difficult to appreciate the mechanism by which the latter structure could be converted into a purpurogallin methyl ether, and formula (V; R = Me) which Willstätter and Heiss suggest for the monomethyl ether is clearly impossible on the basis of the intermediate formation of either (II; R = H, R′ = Me) or (II; R = Me, R′ = H). In order to obtain experimental evidence bearing on the structure of the purpurogallin monomethyl ether we proposed to ethylate, oxidise, and locate the methyl ether group by identification of the resultant diethoxymethoxyphthalic acid. Unfortunately satisfactory ethylation of purpurogallin monomethyl ether was not realised, but an alternative solution of the problem was found. 3-Ethoxy-1 : 2-dihydroxybenzene, prepared in 61% yield by the action of alkaline hydrogen peroxide on 3-ethoxy-2-hydroxybenzaldehyde, like the corresponding

3-methoxy-derivative, could not be oxidised to a purpurogallin derivative but, in the presence of excess of pyrogallol, oxidation to purpurogallin 2′-ethyl ether, m. p. 157°, was effected in 48% yield by means of potassium iodate. This structure (VI; R = R″ = R‴ = H, R′ = Et) was established by methylation to 2′-ethoxy-3′ : 4′ : 4-trimethoxybenzo*cyclo*heptatrien-3-one (VI; R = R″ = R‴ = Me; R′ = Et), m. p. 91—92°, which was oxidised by permanganate to 5-ethoxy-3 : 4-dimethoxyphthalic acid (VIII), giving an anhydride, m. p. 127°, and a *N*-methylimide, m. p. 122°. The acid (VIII) differed from the known 3-ethoxy-4 : 5-dimethoxyphthalic acid (Späth, *Ber.*, 1932, **65**, 1778; Späth and Becke, *ibid.*, 1934, **67**, 2100; Manske and Holmes, *J. Amer. Chem. Soc.*, 1945, **67**, 95; Manske, Ledingham, and Holmes, *Canad. J. Res.*, 1945, **23**, B, 100) and 4-ethoxy-3 : 5-dimethoxyphthalic acid (Manske, Ledingham, and Holmes, *loc. cit.*), but was identified by comparison with a synthetic sample of 5-ethoxy-3 : 4-dimethoxyphthalic acid. The most attractive route to this acid (VIII) seemed to be from 5-ethoxy-6-methoxyphthalide (IX), prepared in an analogous manner to *m*-meconine (Rây and Robinson, *J.*, 1925, **127**, 1618), by nitration, reduction to (X), diazotisation, replacement of the amino-group by hydroxyl, methylation, and oxidation to (VIII). Rây and Robinson (*loc. cit.*)

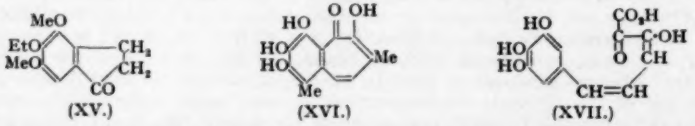

(VII.) (VIII.) (IX.) (X.)

showed that *m*-meconine was nitrated in position 7, and 5-ethoxy-6-methoxyphthalide gave, under the same conditions, a mononitro-compound assumed by analogy to be the 7-nitrophthalide. This was reduced to the weakly basic 7-amino-compound (X); this was diazotised in glacial acetic acid but the diazo-group was not replaced by hydroxyl under the conditions employed and the route was abandoned.

Pacsu (*Ber.*, 1923, **56**, 407) described the preparation of 4-hydroxy-2 : 3-dimethoxybenzoic acid, m. p. 154—155°, by the following reactions :


(XI.) (XII.) (XIII.) (XIV.)

Although Pacsu emphasised the absence of migration of the *p*-benzoyl group during this synthesis, the subsequent reaction of the final product, m. p. 150°, obtained by us, indicated that it was 3-hydroxy-2 : 4-dimethoxybenzoic acid (XIII) instead of (XII). It is suggested that, in our hands, the acid hydrolysis of the 2 : 3-diacetoxy-4-benzoyloxybenzoic acid yielded 3-benzoyloxy-2 : 4-dihydroxybenzoic acid, m. p. 227° (decomp.) (XIV), instead of (XI) for which Pacsu gives m. p. 210° (decomp.), and we failed to reacetylate our product to 2 : 3-diacetoxy-4-benzoyloxybenzoic acid. The acid (XIII), which gave a blue colour with 2 : 6-dichloroquinone chloroimide, was ethylated to 3-ethoxy-2 : 4-dimethoxybenzoic acid, m. p. 89°, but attempts to convert this into a phthalide derivative either by formaldehyde and hydrochloric acid or by chloral and sulphuric acid were unsuccessful; Manske, Ledingham, and Holmes (*loc. cit.*) encountered a similar failure with 2 : 3 : 4-trimethoxybenzoic acid. The acid, m. p. 89°,


(XV.) (XVI.) (XVII.)

was therefore reduced with lithium aluminium hydride to 3-ethoxy-2 : 4-dimethoxybenzyl alcohol which was oxidised with chromic acid to 3-ethoxy-2 : 4-dimethoxybenzaldehyde. This

aldehyde was condensed with malonic acid in pyridine in the presence of piperidine to yield 3-ethoxy-2 : 4-dimethoxycinnamic acid, which was reduced and converted into 5-ethoxy-4 : 6-dimethoxyindanone (XV). Permanganate oxidation of (XV) gave 4-ethoxy-3 : 5-dimethoxyphthalic acid which yielded an anhydride, m. p. 116°, and a *N*-methylimide, m. p. 124°, identical with authentic specimens prepared as described by Manske, Ledingham, and Holmes (*loc. cit.*).

The successful synthesis of 5-ethoxy-3 : 4-dimethoxyphthalic acid was based upon the claim of Mauthner (*J. pr. Chem.*, 1938, **150**, 257) to have prepared 2 : 3-dihydroxy-4-methoxybenzaldehyde from 1 : 2-dihydroxy-3-methoxybenzene. In a similar way 4-ethoxy-2 : 3-dihydroxybenzaldehyde is obtained by the action of zinc cyanide and hydrogen chloride on 3-ethoxy-1 : 2-dihydroxybenzene, and the constitution of this *o*-hydroxy-aldehyde was established by its conversion into 7-ethoxy-8-hydroxycoumarin. Methylation of the *o*-hydroxy-aldehyde gave 4-ethoxy-2 : 3-dimethoxybenzaldehyde which was converted *via* 4-ethoxy-2 : 3-dimethoxycinnamic acid, the corresponding phenylpropionic acid, and 6-ethoxy-4 : 5-dimethoxyindanone into 5-ethoxy-3 : 4-dimethoxyphthalic acid (VIII), which was shown by comparison of the anhydride and *N*-methylimide to be identical with the product obtained from 2'-ethoxy-3' : 4' : 4-trimethoxybenzo*cyclo*heptatrien-3-one (VI; R = R'' = R''' = Me, R' = Et).

The formation of purpurogallin 2'-ethyl ether (VI; R = R'' = R''' = Me, R' = Et) from pyrogallol and 3-ethoxy-1 : 2-dihydroxybenzene is entirely consistent with the mechanism suggested on p. 1319. Oxidation would lead to 3-ethoxy- and 3-hydroxy-1 : 2-benzoquinone, and in view of the reduced anionoid reactivity (or the inability to tautomerise to a triketo-form), the former will function as the cationoid component and favour the production of the ethoxy-*o*-diphenoquinone (III; R = Et); the isomer is unlikely to be found as the ethoxy-group will reduce the cationoid properties at position 4 more than at position 5. Observation on the formation of purpurogallin-carboxylic acid reported in Part VII of this series (see following paper) also confirms the mechanism now proposed. Further support is obtained from some preliminary experiments with 2 : 3 : 4-trihydroxytoluene which yields a dimethylpurpurogallin, probably 4 : 2' : 3' : 4'-tetrahydroxy-5 : 1'-dimethylbenzo*cyclo*heptatrien-3-one (XVI), on oxidation with potassium iodate. These and other experiments suggested by the new mechanism will be described in later communications.

At the moment we are unable to bring forward any experimental evidence bearing on the mechanism of the conversion of the *o*-diphenoquinone (III; R = H) into purpurogallin, but theoretical objections to the postulated benzilic acid rearrangement may be mentioned. Although some benzilic acid rearrangements are known to occur under weakly alkaline conditions (for example, see Malkin and Robinson, *J.*, 1925, **127**, 369), purpurogallin is produced in a neutral or faintly acidic medium, and the usual hydroxyl-ion-catalysed mechanism is unlikely to operate under these conditions. Secondly, steric conditions would appear unfavourable for the production of the appropriate transition complex between the quinonoid group and position *y* in the *o*-diphenoquinone (III; R = H). In view of these objections to the benzilic acid mechanism propounded by Willstätter and Heiss (*loc. cit.*), the following alternative explanation of the conversion of (III; R = H) into purpurogallin is more attractive. The *o*-diphenoquinone (III; R = H), in the form of its tautomeric triketonic structure, represents the vinyl analogue of a β-diketone, and consequently acid hydrolysis to (XVII), followed by cyclisation and loss of the elements of formic acid to yield purpurogallin (VI; R = R' = R'' = R''' = H), are not unreasonable propositions.

Experimental.

3 : 4 : 5-Trimethoxyaniline, required for the preparation of 5-iodo-1 : 2 : 3-trimethoxybenzene, was obtained by a modification of Graebe and Suter's method (*loc. cit.*) employing sodium hypochlorite instead of hypobromite, which in our hands yielded a brominated product. A solution of sodium hypochlorite was prepared by passing chlorine [from potassium permanganate (12·36 g.) and concentrated hydrochloric acid (78 c.c.)] into an ice-cold solution of sodium hydroxide (48 g.) in water (300 c.c.) and ice (200 g.). 3 : 4 : 5-Trimethoxybenzamide (Harding, *J.*, 1911, **99**, 1593) (39 g.) was added and the mixture shaken for 2 hours. The temperature of the mixture was raised with stirring to 70° during 1 hour and kept at this temperature for a further hour. Sodium hydroxide solution (72 g. in 72 c.c. of water) was then slowly added to the red-brown solution, the temperature was raised to 80°, and after 1 hour the amine which separated was collected and dried *in vacuo* (yield, 20 g.).

3 : 3-*Dimethyl*-1-(3 : 4 : 5-*trimethoxyphenyl*)*triazen* (VII).—3 : 4 : 5-Trimethoxyaniline (0·35 g.) was diazotised by dissolving it in dilute hydrochloric acid (8·5 c.c.), cooling to 0°, and adding a solution of sodium nitrite (0·135 g.) in water (5 c.c.). The resultant solution was added to a cold mixture of 33% aqueous dimethylamine (1·4 c.c.) and 10% aqueous sodium carbonate (13 c.c.). After half an hour at room temperature the *triazen* was collected; it crystallised from light petroleum (b. p. 60—80°) (charcoal) in colourless stout needles, m. p. 97—98° (Found: N, 17·5. $C_{11}H_{17}O_3N_3$ requires N, 17·6%).

2 : 3 : 4 : 3′ : 4′ : 5′-*Hexamethoxydiphenyl.*—Freshly precipitated copper powder (14 g.) was added to a mixture of 4- and 5-iodo-1 : 2 : 3-trimethoxybenzene (7 g. of each) heated at 250°, and the temperature slowly raised to 270°. After 15 minutes the molten mass was cooled, the sticky product was extracted with ethyl alcohol and filtered off, and the filtrate concentrated to 10 c.c. and cooled. The solid (A) which separated was collected and washed with alcohol, the filtrate and washings were concentrated to 4 c.c., and the process was repeated. Alcohol was removed completely from the combined concentrate, leaving a brown gum (2·3 g.) which was distilled under reduced pressure. 2 : 3 : 4 : 3′ : 4′ : 5′-Hexamethoxydiphenyl was obtained as a yellow oil (b. p. 215—220°/0·05 mm.) which crystallised from alcohol in colourless irregular prisms (1·7 g.), m. p. 89° (Found : C, 64·9; H, 6·5. $C_{18}H_{22}O_6$ requires C, 64·7; H, 6·6%). The solid material (A) which separated from the crude product was resolved by fractional crystallisation from ethyl alcohol into 2 : 3 : 4 : 2′ : 3′ : 4′-hexamethoxydiphenyl (1·5 g.), m. p. 122°, and 3 : 4 : 5 : 3′ : 4′ : 5′-hexamethoxydiphenyl (1·5 g.), m. p. 128°, the former being the less soluble.

2 : 3 : 4 : 3′ : 4′ : 5′-*Hexahydroxydiphenyl* (II; R = R′ = H).—2 : 3 : 4 : 3′ : 4′ : 5′-Hexamethoxydiphenyl (1·4 g.) was heated under reflux with 48% hydrobromic acid (25 c.c.) for 30 minutes. Concentration to half bulk and cooling yielded 2 : 3 : 4 : 3′ : 4′ : 5′-*hexahydroxydiphenyl* (0·45 g.) which crystallised from water containing a little sulphur dioxide in white needles, m. p. >300° (Found : C, 57·4; H, 4·2. $C_{12}H_{10}O_6$ requires C, 57·6; H, 4·0%). Warming with excess of acetic anhydride and fused sodium acetate for 15 minutes, followed by dilution with water, gave 2 : 3 : 4 : 3′ : 4′ : 5′-*hexa-acetoxydiphenyl* which crystallised from alcohol in irregular prisms, m. p. 167° (Found : C, 57·2; H, 4·6; CH_3·CO, 51·4. $C_{24}H_{22}O_{12}$ requires C, 57·4; H, 4·4; CH_3·CO, 50·8%).

Purpurogallin 2′-Methyl Ether (VI; R = R″ = R‴ = H; R′ = Me) was prepared from 1 : 2-dihydroxy-3-methoxybenzene and pyrogallol by Willstätter and Heiss's method (*loc. cit.*) or preferably by the action of potassium iodate on the mixture. After sublimation of the crude product at 200°/0·05 mm., crystallisation from chloroform yielded deep red needles, m. p. 193° (Found : C, 61·8; H, 4·2. Calc. for $C_{12}H_{10}O_5$: C, 61·6; H, 4·3%). Willstätter and Heiss give m. p. 182—183°.

3-*Ethoxy*-1 : 2-*dihydroxybenzene.*—3-Ethoxy-2-hydroxybenzaldehyde (8·3 g.) was stirred in an atmosphere of nitrogen with N-sodium hydroxide (50 c.c.) at 40° until dissolution was complete. Hydrogen peroxide (35·5 c.c. of 20-vol.) was added in 5-c.c. portions; the addition of the last few drops caused precipitation of a fawn-coloured solid which was collected, dried, and crystallised from light petroleum (b. p. 60—80°). The product (4·7 g.; 61%) had m. p. 91—93° and showed no depression when mixed with a sample of 3-ethoxy-1 : 2-dihydroxybenzene prepared as described by Haworth and Lamberton (*J.*, 1946, 1003).

Purpurogallin 2′-Ethyl Ether (VI; R = R″ = R‴ = H, R′ = Et).—Pyrogallol (0·8 g.) and potassium iodate solution (24 c.c. of 5·77%) were added successively to a solution of 3-ethoxy-1 : 2-dihydroxybenzene (4·0 g.) in water (200 c.c.). After 15 minutes the brown precipitate was collected and further pyrogallol (0·6 g.) and potassium iodate solution (18 c.c. of 5·77%) were added to the filtrate. The process was repeated four times, pyrogallol (0·5, 0·4, 0·3, 0·3 g.) and potassium iodate solution (15, 12, 9, and 9 c.c. of 5·77%) being added alternately. The total yield of dry brown solid was 5·9 g., having m. p. 120—130°. Sublimation at 170—180°/0·05 mm. yielded a bright red solid (3·1 g.) which crystallised from damp acetone with water of crystallisation and had m. p. 157° (Found : C, 58·8; H, 5·3. $C_{13}H_{12}O_5,H_2O$ requires C, 58·8; H, 5·8%).

Purpurogallin 2′-Ethyl 3′ : 4-Dimethyl Ether (VI; R‴ = H, R′ = Et, R = R″ = Me).—Purpurogallin 2′-ethyl ether (3·0 g.) was dissolved in pure dioxan (20 c.c.), and a solution of diazomethane (1·3 g.) in ether (85 c.c.) added. After 12 hours the yellow *product* which separated was collected and crystallised from alcohol; it formed fibrous yellow needles (1·9 g.), m. p. 161° (Found : C, 65·5; H, 5·7. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8%), which dissolved readily in sodium hydroxide solution and gave an olive-brown ferric colour. Concentration of the mother-liquors yielded *purpurogallin 2′-ethyl 3′(or 4)-methyl ether* (0·5 g.) which crystallised from alcohol in deep yellow needles, m. p. 128° (Found : C, 64·2; H, 5·2. $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·3%), dissolved in sodium hydroxide solution, and gave a wine-red ferric test.

Purpurogallin 2′-Ethyl 3′ : 4′ : 4-Trimethyl Ether (VI; R′ = Et, R = R″ = R‴ = Me).—Methyl sulphate (3·6 c.c.) was added to a finely powdered suspension of purpurogallin 2′-ethyl 3′ : 4-dimethyl ether (1·26 g.) in 65% potassium hydroxide solution (8 c.c.), and the mixture heated gently with constant shaking until a vigorous reaction set in which was allowed to become complete without further heating. After cooling and dilution with water, the brown oil which separated and quickly solidified was collected, dried, and crystallised from *cyclo*hexane; colourless plates (1·1 g.), m. p. 91—92° (Found : C, 65·9; H, 6·0. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·2%), were obtained.

Oxidation of Purpurogallin 2′-Ethyl 3′ : 4′ : 4-Trimethyl Ether (VI; R′ = Et, R = R″ = R‴ = Me).—Purpurogallin 2′-ethyl 3′ : 4′ : 4-trimethyl ether (0·8 g.) was dissolved in pure acetone (20 c.c.), and 2% aqueous potassium permanganate (120 c.c.) added portionwise. After 3 hours' shaking the mixture was filtered, and the filtrate made strongly alkaline with sodium hydroxide (10 g.) and concentrated to 15 c.c. Cooling and acidification with concentrated hydrochloric acid gave a precipitate of sodium chloride, which was collected, and the filtrate was extracted six times with ether. The dried ethereal extract was concentrated and the brown oily residue on distillation at 180°/0·05 mm. yielded a yellow oil (0·2 g.) which after crystallisation first from chloroform–ether and then from ether gave 5-*ethoxy*-3 : 4-*dimethoxyphthalic anhydride* (0·08 g.) as white needles, m. p. 127° (Found : C, 57·6; H, 4·7. $C_{12}H_{12}O_6$ requires C, 57·2; H, 4·8%) undepressed on mixture with a synthetic specimen (p. 1325) This anhydride (0·03 g.) on treatment with excess of 30% methylamine solution, evaporation to dryness, heating at 180°/12 mm. and sublimation at 160°/0·05 mm. gave 5-*ethoxy*-3 : 4-*dimethoxy*-N-*methylphthalimide* (0·025 g.) which crystallised from aqueous methanol in long shining needles, m. p. 122° (Found : C, 58·9; H, 5·8; N, 5·3. $C_{13}H_{15}O_5N$ requires C, 58·9; H, 5·7; N, 5·3%) undepressed on admixture with a synthetic specimen.

4-Ethoxy-3-methoxybenzoic Acid.—A stream of carbon dioxide was passed through a stirred suspension of 4-ethoxy-3-methoxybenzaldehyde (40 g.) [prepared from vanillin as described by Tiemann (*Ber.*, 1875, **8**, 1128)] in water (300 c.c.) at 70°. Potassium permanganate (25·1 g.) in water (500 c.c.) was slowly added and the stirring continued for half an hour after the addition was complete. The reaction mixture was filtered and rendered alkaline and the neutral impurities were removed in ether. Acidification of the alkaline layer precipitated 4-ethoxy-3-methoxybenzoic acid (28 g.) which crystallised from alcohol in colourless plates, m. p. 192°. Tiemann (*loc. cit.*) gives m. p. 193—194°

5-Ethoxy-6-methoxyphthalide (IX).—Concentrated hydrochloric acid (40 c.c.) and 40% formaldehyde solution (12 c.c.) were added to a solution of 4-ethoxy-3-methoxybenzoic acid (10·84 g.) in acetic acid (85 c.c.) and heated on the water-bath for 12 hours. After addition of charcoal, the mixture was filtered, concentrated to 40 c.c., made alkaline with potassium hydroxide, and filtered again. The alkaline solution was acidified with concentrated hydrochloric acid, boiled for 10 minutes, and cooled and the mixture of acid and lactone collected and washed with sodium hydrogen carbonate solution. The residual *lactone* (5 g.), after being dried and sublimed at 170°/0·1 mm., crystallised from alcohol in small colourless prisms, m. p. 187·5—188·5° (Found: C, 63·7; H, 6·0. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%).

5-Ethoxy-6-methoxy-7-nitrophthalide.—Finely powdered 5-ethoxy-6-methoxyphthalide (IX) (7·55 g.) was added in small portions, with shaking, during 20 minutes to concentrated nitric acid (16 c.c.) cooled to 5°. The mixture was kept at 3—5° for a further 2 hours and then allowed to reach room temperature during 1 hour. Water (100 c.c.) was added and the precipitate was collected, dried, and extracted with boiling alcohol (25 c.c.). The residue crystallised from glacial acetic acid in small colourless needles (5·6 g.), m. p. 169° (Found: C, 52·15; H, 4·3; N, 5·0. $C_{11}H_{11}O_6N$ requires C, 52·15; H, 4·3; N, 5·5%).

7-Amino-5-ethoxy-6-methoxyphthalide (X).—To a hot solution of crystalline stannous chloride (3·07 g.) in concentrated hydrochloric acid (5·7 c.c.) was added portionwise 5-ethoxy-6-methoxy-7-nitrophthalide (1·02 g.). After 10 minutes' heating on a water-bath a further addition of stannous chloride (0·3 g.) and concentrated hydrochloric acid (1 c.c.) effected complete dissolution of the nitro-compound. The solution was heated for half an hour, then added to cold water (25 c.c.), and the precipitated solid was collected, washed with sodium hydrogen carbonate solution, and dried. Crystallisation from absolute alcohol gave the amine (X) as long hair-like colourless needles (0·71 g.), m. p. 151° (Found: C, 59·4; H, 5·6; N, 6·6. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·8; N, 6·3%).

2 : 3 : 4-*Trihydroxybenzoic Acid.*—The method of Baker and Smith (*J.*, 1931, 2544) gave poor yields of inferior material in our hands, but the following modification raised the yield to 70—90% of pure acid. A paste of finely powdered pyrogallol (100 g.), potassium hydrogen carbonate (200 g.), and water (50 c.c.) was heated under a stream of carbon dioxide in an oil-bath at 90°. The bath-temperature was raised to 135° during 2 hours, and kept thereat until water was no longer evolved or until the violet-coloured mixture began to char at the edges. After cooling, the product was dissolved in water (1 l.) and acidified with hydrochloric acid, and the 2 : 3 : 4-trihydroxybenzoic acid (90—110 g.), m. p. 210° (decomp.), was collected. Schiff (*Annalen*, 1888, **245**, 37) gives m. p. 206—208°.

3-*Benzoyloxy*-2 : 4-*dihydroxybenzoic Acid* (XIV).—2 : 3-Diacetoxy-4-benzoyloxybenzoic acid (30 g.), prepared by Pacsu's method (*loc. cit.*), was dissolved in acetic acid (75 c.c.) and heated on the water-bath for 3 hours with 5N-hydrochloric acid (75 c.c.). Cooling and filtration yielded a fawn-coloured solid (8 g.), m. p. 227° (decomp.), and a further crop (6 g.) was obtained by cooling the mother-liquors at 0° for 12 hours. Crystallisation from methanol gave 3-*benzoyloxy*-2 : 4-*dihydroxybenzoic acid* as white plates, m. p. 227° (decomp.) (Found: C, 61·3; H, 3·8. $C_{14}H_{10}O_5$ requires C, 61·4; H, 3·7%).

3-*Hydroxy*-2 : 4-*dimethoxybenzoic Acid* (XIII).—3-Benzoyloxy-2 : 4-dihydroxybenzoic acid (12·8 g.) in acetone (50 c.c.) was treated with diazomethane (6·45 g.) in ether (300 c.c.) for 48 hours at room temperature. Removal of excess of diazomethane and solvents yielded crude methyl 3-benzoyloxy-2 : 4-dimethoxybenzoate (16·3 g.). The ester was dissolved in methanol (140 c.c.) and, after displacement of air in the reaction vessel with hydrogen, 5N-sodium hydroxide (56 c.c.) was added and the mixture kept at 45° for 6 hours. It was then cooled, acidified with hydrochloric acid, and evaporated to dryness; extraction with acetone gave a brown oil from which benzoic acid was removed by exhaustive extraction with light petroleum (b. p. 40—60°). The residue on crystallisation from hot water gave 3-*hydroxy*-2 : 4-*dimethoxybenzoic acid* as white rhombs, m. p. 150° with previous softening (Found: C, 54·2; H, 4·8. $C_9H_{10}O_5$ requires C, 54·6; H, 5·0%).

3-*Ethoxy*-2 : 4-*dimethoxybenzoic Acid.*—3-Hydroxy-2 : 4-dimethoxybenzoic acid (3·45 g.) in 10% sodium hydroxide solution (15·3 c.c.) was refluxed for 30 minutes during the dropwise addition of ethyl sulphate (7·65 c.c.) and 10% sodium hydroxide solution (25·3 c.c.). Further quantities of ethyl sulphate (5·0 c.c.) and 20% sodium hydroxide solution (7·65 c.c.) were added after 1 hour and, after boiling for another 20 minutes, the mixture was concentrated to half volume, treated with charcoal, and filtered. The cooled filtrate on acidification with hydrochloric acid yielded 3-*ethoxy*-2 : 4-*dimethoxybenzoic acid* (3·4 g.) which crystallised from hot water, containing a little alcohol, in long colourless needles, m. p. 89—90° (Found: C, 58·5; H, 6·2. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%).

3-*Ethoxy*-2 : 4-*dimethoxybenzyl Alcohol.*—To a cooled solution of lithium aluminium hydride (1·5 g.) in ether (50 c.c.), 3-ethoxy-2 : 4-dimethoxybenzoic acid (1·3 g.) in ether (10 c.c.) was added dropwise, and after 3 hours at room temperature the mixture was refluxed for half an hour. After decomposition with 2N-sulphuric acid, the ethereal layer was washed with sodium hydrogen carbonate solution and dried, and the solvent removed. The residual 3-*ethoxy*-2 : 4-*dimethoxybenzyl alcohol* (1·0 g.) had b. p. 120°/0·05 mm. (Found: C, 62·5; H, 7·4. $C_{11}H_{16}O_4$ requires C, 62·3; H, 7·5%). The 3 : 5-*dinitrobenzoate* crystallised from benzene–light petroleum (b. p. 60—80°) in pale yellow needles, m. p. 116° (Found: C, 53·4; H, 4·4; N, 7·2. $C_{18}H_{16}O_9N_2$ requires C, 53·2; H, 4·4; N, 6·9%).

3-*Ethoxy*-2 : 4-*dimethoxybenzaldehyde*.—3-Ethoxy-2 : 4-dimethoxybenzyl alcohol (1·0 g.) in glacial acetic acid (13·2 c.c.) and water (1·05 c.c.) was oxidised with chromium trioxide (0·33 g.) in glacial acetic acid (8 c.c.) and water (1·05 c.c.) at 15°. After 1 hour the mixture was poured on ice (20 g.), neutralised with concentrated aqueous ammonia, and extracted with ether; the extract, after being washed with sodium hydrogen carbonate solution, dried, and freed from solvent, yielded a brown oily *aldehyde*. Distillation gave a yellow oil (0·67 g.), b. p. 140°/0·05 mm. (Found: C, 63·1; H, 6·3. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate–ethyl alcohol in deep scarlet rhombs, m. p. 170° (Found: C, 52·1; H, 4·4; N, 14·4. $C_{17}H_{18}O_7N_4$ requires C, 52·3; H, 4·6; N, 14·4%).

3-*Ethoxy*-2 : 4-*dimethoxycinnamic Acid*.—3-Ethoxy-2 : 4-dimethoxybenzaldehyde (0·58 g.) was dissolved in pyridine (1·3 c.c.) and piperidine (0·05 c.c.). Malonic acid (0·6 g.) was added and the mixture was heated under reflux for 2 hours on the water-bath, the reaction being completed by boiling the solution for 2 minutes. The mixture was poured on ice (20 g.) and 2N-hydrochloric acid (20 c.c.); the precipitate was collected and crystallised from 10% alcohol; 3-*ethoxy*-2 : 4-*dimethoxycinnamic acid* (0·40 g.) was obtained in clusters of long needles, m. p. 159° (Found: C, 61·8; H, 6·0. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·3%).

β-(3-*Ethoxy*-2 : 4-*dimethoxyphenyl*)*propionic Acid*.—3-Ethoxy-2 : 4-dimethoxycinnamic acid (0·35 g.), dissolved in pure methanol (6 c.c.), was shaken under hydrogen with 10% palladium–charcoal (0·035 g.). Hydrogen uptake was complete in 1 hour, and after removal of catalyst and solvent the residual *acid* crystallised from light petroleum (b. p. 60—80°) in colourless plates, m. p. 51° (Found: C, 61·8; H, 6·9. $C_{13}H_{18}O_5$ requires C, 61·6; H, 7·1%).

4-*Ethoxy*-3 : 5-*dimethoxyphthalic Anhydride*.—β-(3-Ethoxy-2 : 4-dimethoxyphenyl)propionic acid (0·29 g.) in benzene (6 c.c.) was heated on the water-bath for 2 hours with phosphoric oxide (1·2 g.). The purple complex was decomposed with ice (40 g.) and after 12 hours the mixture was extracted with ether, the ethereal extract was washed successively with N-sodium hydroxide solution and water and dried, and the solvent removed. 5-Ethoxy-4 : 6-dimethoxyindanone (XV) (0·19 g.) was obtained as a yellow oil which was oxidised without further purification. 2% Potassium permanganate solution (40 c.c.) was added gradually to a warm suspension of the indanone (0·19 g.) in water (10 c.c.). When oxidation was complete, manganese dioxide was removed, the filtrate rendered alkaline with sodium hydroxide (4 g.), and neutral material removed with ether. The aqueous layer was concentrated to 10 c.c., cooled, acidified with concentrated hydrochloric acid, and extracted 6 times with ether; the dried extract yielded a brown oil (0·14 g.) which distilled at 200°/0·05 mm. and crystallised from chloroform–ether in needles, m. p. 116°, undepressed on admixture with an authentic specimen of 4-ethoxy-3 : 5-dimethoxyphthalic anhydride, prepared by the method of Manske, Ledingham, and Holmes (*loc. cit.*). The *N*-methylimide, prepared in the usual way, had m. p. 124°, undepressed on admixture with an authentic sample.

4-*Ethoxy*-2 : 3-*dihydroxybenzaldehyde*.—This was prepared by a slight modification of Mauthner's method (*loc. cit.*). 3-Ethoxy-1 : 2-dihydroxybenzene (15 g.) in ether (150 c.c.) was stirred with powdered zinc cyanide (36·3 g.) during passage of a steady stream of hydrogen chloride. The ether was decanted from the pink paste of aldimine hydrochloride which was shaken with ice-cold water (150 c.c.), and the resultant solution was extracted immediately with several 50-c.c. portions of ether. These extracts yielded unchanged 3-ethoxy-1 : 2-dihydroxybenzene (10·5 g.). The aqueous solution was boiled for 2 minutes and the *aldehyde* isolated with ether as a dark brown oil (4 g.), which solidified on addition of a little water and crystallised from hot water (150 c.c.) (charcoal) in pale yellow needles, m. p. 98° (Found: C, 58·5; H, 5·6. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%). The *anil* crystallised from ethanol in groups of irregular scarlet needles, m. p. 142° (Found: C, 70·0; H, 6·0; N, 5·6. $C_{15}H_{15}O_3N$ requires C, 70·1; H, 5·8; N, 5·45%).

7-*Ethoxy*-8-*hydroxycoumarin*.—4-Ethoxy-2 : 3-dihydroxybenzaldehyde (0·42 g.), fused sodium acetate (0·8 g.), and acetic anhydride (2·5 c.c.) were heated at 120° for 2 hours and then at 180° for 6 hours. The cooled product was diluted with water (10 c.c.) and extracted with ether; the dried extract on evaporation yielded a brown oil (0·58 g.) which was refluxed for 10 minutes with methanol (12 c.c.) and concentrated hydrochloric acid (6 c.c.). The solution was diluted with water and the product, isolated with ether, was sublimed at 160°/0·05 mm. 7-Ethoxy-8-hydroxycoumarin (0·1 g.) crystallised from light petroleum (b. p. 60—80°) in colourless needles, m. p. 144°. Wessely and Sturm (*Ber.*, 1929, **62**, 115) give m. p. 145°.

4-*Ethoxy*-2 : 3-*dimethoxybenzaldehyde*.—A solution of 4-ethoxy-2 : 3-dihydroxybenzaldehyde (2 g.) in acetone (30 c.c.) was refluxed with potassium carbonate (8 g.) and methyl iodide (10 c.c.) for 8 hours; after 2 hours more methyl iodide (5 c.c.) was added and after 4 hours potassium carbonate (8 g.) and methyl iodide (5 c.c.) were added. The mixture was filtered and the filtrate concentrated and shaken with ether (50 c.c.) and water (50 c.c.). The ethereal extract was washed with N-sodium hydroxide, dried and concentrated; 4-*ethoxy*-2 : 3-*dimethoxybenzaldehyde* was obtained as a yellow oil (2·1 g.), b. p. 140°/0·5 mm. (Found: C, 62·7; H, 6·5. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* crystallised from a mixture of ethyl acetate and methyl alcohol in irregular orange plates with a golden lustre, m. p. 158·5° (Found: C, 52·5; H, 4·7; N, 14·4. $C_{17}H_{18}O_7N_4$ requires C, 52·3; H, 4·6; N, 14·4%).

4-*Ethoxy*-2 : 3-*dimethoxybenzoic Acid*.—A solution of 4-ethoxy-2 : 3-dimethoxybenzaldehyde (0·06 g.) in acetone (2 c.c.) was oxidised with potassium permanganate (1·5 c.c. of 5% solution) on the water-bath for 1 hour. The mixture was filtered, the filtrate rendered alkaline, concentrated, and acidified with hydrochloric acid, and the acid collected. Crystallisation from hot water gave 4-*ethoxy*-2 : 3-*dimethoxybenzoic acid* in colourless prisms, m. p. 89° (Found: C, 58·5; H, 6·5. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%). The m. p. was depressed 20° on admixture with 3-ethoxy-2 : 4-dimethoxybenzoic acid (m. p. 89°) or with 2-ethoxy-3 : 4-dimethoxybenzoic acid (m. p. 79°).

4-Ethoxy-2 : 3-dimethoxycinnamic acid, prepared from 4-ethoxy-2 : 3-dimethoxybenzaldehyde (2 g.), malonic acid (2 g.), pyridine (4 c.c.), and piperidine (3 drops) in the manner described for 3-ethoxy-2 : 4-dimethoxycinnamic acid, crystallised from 10% alcohol in fibrous white needles, m. p. 183° (Found : C, 62·0; H, 6·8. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%).

β-(4-Ethoxy-2 : 3-dimethoxyphenyl)propionic acid, prepared by catalytic reduction of 4-ethoxy-2 : 3-dimethoxycinnamic acid (1·9 g.) in methanol (40 c.c.) in presence of 10% palladium–charcoal (0·2 g.) in the manner described previously, crystallised from light petroleum (b. p. 60—80°) in colourless plates, m. p. 68° (Found : C, 61·3; H, 7·0. $C_{13}H_{18}O_5$ requires C, 61·4; H, 7·1%).

5-Ethoxy-3 : 4-dimethoxyphthalic Anhydride.—β-(4-Ethoxy-2 : 3-dimethoxyphenyl)propionic acid (1·9 g.), dissolved in benzene (40 c.c.), was heated with phosphoric oxide (8 g.) for 2 hours and the product isolated as described above. 6-Ethoxy-4 : 5-dimethoxyindanone (1·1 g.), isolated as described previously for an analogous case, was an oil, which was oxidised with 2% potassium permanganate solution (400 c.c.). The mixture was filtered, and the filtrate rendered alkaline, concentrated, acidified, and extracted with ether. The dried concentrated extract yielded on distillation 5-ethoxy-3 : 4-dimethoxyphthalic anhydride (0·2 g.), b. p. 200°/0·05 mm., which crystallised first from chloroform–hexane, then from ether, in pale yellow needles, m. p. 127°, undepressed on admixture with the anhydride obtained from purpurogallin 2′-ethyl 3′ : 4′ : 4-trimethyl ether. The *N*-methylimide, m. p. 122°, was not depressed on admixture with the *N*-methylimide prepared from purpurogallin 2′-ethyl 3′ : 4′ : 4-trimethyl ether.

Oxidation of 2 : 3 : 4-Trihydroxytoluene.—2 : 3 : 4-Trihydroxytoluene (0·74 g.), prepared by the method of Majima and Okazaki (*Ber.*, 1916, **49**, 1482), was dissolved in ice-cold water (15 c.c.), and ice-cold potassium iodate solution (10 c.c. of 5·77%) was added dropwise. After 15 minutes at room temperature, the orange *2 : 3 : 4 : 4′-tetrahydroxy-1′ : 5-dimethylbenzocycloheptatrien-3-one* (XVI) (0·42 g.) was collected, dried *in vacuo*, and sublimed at 170°/0·1 mm. as a yellow micro-crystalline powder, m. p. 185° (Found : C, 62·8; H, 4·9. $C_{13}H_{12}O_5$ requires C, 63·0; H, 4·8%).

We thank the Department of Scientific and Industrial Research for a maintenace grant to A. C., the University for the award of a Henry Ellison Fellowship to P. L. P., Dr. R. H. Manske for a specimen of 3-ethoxy-4 : 5-dimethoxyphthalic anhydride, Sir Robert Robinson, F.R.S., for a generous gift of 3-ethoxy-2-hydroxybenzaldehyde, and the Imperial Chemical Industries Limited for a grant towards the expenses of the research.

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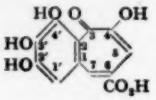
293. *Purpurogallin. Part VII. Constitution of Purpurogallin-carboxylic Acid.*

By WILFRID D. CROW and ROBERT D. HAWORTH.

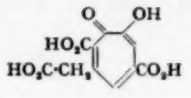
An improved preparation of purpurogallin-carboxylic acid (I) from a mixture of gallic acid and pyrogallol is described, and the structure of the acid has been established (*a*) by oxidation of its tetramethyl ether with permanganate to 3 : 4 : 5-trimethoxyphthalic anhydride and (*b*) by oxidation with alkaline hydrogen peroxide to αβ′-dicarboxy-β-carboxymethyltropolone (II). The latter acid on decarboxylation gave β-methyltropolone-β′-carboxylic acid (III), which was converted into uvitic acid (IV) by fusion with potassium hydroxide.

OXIDATION of gallic acid with potassium ferricyanide in presence of aqueous sodium acetate, or preferably electrolytically in sodium sulphate or acetate solution has been shown to give purpurogallin-carboxylic acid, $C_{12}H_8O_7$ (Perkin and Stevens, *J.*, 1903, **83**, 192; Perkin and Perkin, *J.*, 1904, **85**, 243; 1908, **93**, 1188). Although a number of ethers and esters of the acid have been described by Perkin *et al.* (*locc. cit.*) and Willstätter and Heiss (*Annalen*, 1923, **433**, 17), no experimental evidence leading to a structural formula for the acid or establishing a relationship with purpurogallin has been published. No doubt the inaccessibility of the acid has handicapped investigation, and in our hands the methods previously reported gave extremely poor yields. Hooker (*Ber.*, 1887, **20**, 3073) obtained a small yield of purpurogallin by the action of sodium nitrite on a solution of gallic acid in aqueous acetic acid, but we failed to confirm this observation, and the action of potassium iodate on gallic acid or ethyl gallate was equally disappointing; some iodine was liberated unless the acid was neutralised before the addition of the iodate, but we failed to discover experimental conditions for the production of purpurogallin-carboxylic acid or its ethyl ester. New views (Part VI, preceding paper) concerning the

mechanism of purpurogallin formation not only explained the difficulties experienced but they indicated (*a*) that purpurogallin-carboxylic acid was probably 4 : 2′ : 3′ : 4′-tetrahydroxybenzo*cyclo*heptatrien-3-one-6-carboxylic acid (I) and (*b*) that a useful preparation might be found in the oxidation of a mixture of pyrogallol and gallic acid with potassium iodate. In practice this reaction proceeded smoothly and after some preliminary experiments concerning the quantities and mode of addition of the reagents it was possible to obtain 22% yields (calculated on the amount of gallic acid employed).



(I.)



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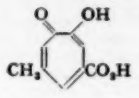

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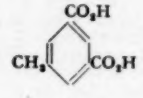

(IV.)

Purpurogallin-carboxylic acid (I), when warmed with methyl alcohol and sulphuric acid, gave a methyl ester, m. p. 267—268° [Willstätter and Heiss, *loc. cit.*, gave m. p. 260—270° (decomp.)], and with methyl sulphate and potassium carbonate in acetone yielded methyl 4 : 2′ : 3′ : 4′-tetramethoxybenzo*cyclo*heptatrien-3-one-6-carboxylate, m. p. 122°, which was hydrolysed by alcoholic potassium hydroxide to the corresponding 4 : 2′ : 3′ : 4′-tetramethoxy-acid, m. p. 185—186° (Perkin and Perkin, *J.*, 1908, **93**, 1188, gave m. p. 182—183°). Methylation with diazomethane gave a phenolic product, probably methyl 4′-hydroxy-2′ : 3′ : 4-trimethoxybenzo*cyclo*heptatrien-3-one-6-carboxylate, m. p. 156—157°, which was hydrolysed to the corresponding acid, m. p. 275—276°, with alcoholic potassium hydroxide. Purpurogallin-carboxylic acid (I) was decarboxylated in boiling quinoline in presence of copper powder, and the product, m. p. 275° (decomp.), was identified as purpurogallin, thus establishing the benzotropolone structure of the acid. The determination of the position of the carboxyl group occupied two stages. First, oxidation of methyl 4 : 2′ : 3′ : 4′-tetramethoxybenzo*cyclo*heptatrien-3-one-6-carboxylate with potassium permanganate gave 3 : 4 : 5-trimethoxyphthalic acid, which we identified by means of the anhydride and *N*-methylimide, and consequently the carboxyl group must reside in the tropolone ring. This was fully confirmed by oxidation of purpurogallin-carboxylic acid (I) with hydrogen peroxide, which gave αβ′-dicarboxy-β-carboxy-methyltropolone (II) in 35% yield. This pale yellow acid was easily decarboxylated either by heating it to its melting point or better by heating it at 250° for a few minutes with a trace of copper powder in dibutyl phthalate. β-Methyltropolone-β′-carboxylic acid (III), m. p. 220—221°, thus obtained, had all the properties of a tropolone derivative, giving a blood-red ferric test, and crimson azo-dyes when coupled with diazo-compounds. When β-methyltropolone-β′-carboxylic acid was heated at 250° with potassium hydroxide it was converted into uvitic acid (IV) which was identified by comparison with an authentic specimen prepared from mesitylene (Fittig and Furtenbach, *Annalen*, 1868, **147**, 296). The yield of uvitic acid was poor (8·4%) but its formation provided rigid proof of the structure of purpurogallin-carboxylic acid (I) and the degradation products (II) and (III).

Experimental.

Purpurogallin-carboxylic Acid (I).—Aqueous solutions of pyrogallol (31 g. in 250 c.c.) and potassium iodate (53 g. in 500 c.c.) were added simultaneously with stirring and ice-cooling to the slurry of sodium gallate obtained by adding gallic acid (47 g.) to a solution of sodium hydrogen carbonate (21 g.) in water (300 c.c.) so that addition of each solution was completed in 45 minutes. After another 15 minutes' stirring, the mixture was acidified with 10*N*-hydrochloric acid (25 c.c.), set aside overnight, and filtered, and the filtrate extracted thrice with ether (total, 1 l.). The air-dried precipitate was extracted several times with hot methyl alcohol (total, 1 l.), the ethereal and alcoholic extracts were combined, and the whole was concentrated until precipitation commenced. The solid was removed, the process was repeated on the filtrate, and the combined solids were washed with methyl alcohol. The air-dried product (29 g.) was an orange microcrystalline powder, recrystallising from dioxan in small orange needles, m. p. above 320° (decomp.) (Found : C, 54·3; H, 3·4. Calc. for $C_{13}H_8O_7$: C, 54·6; H, 3·1%). The acid (I) was readily soluble in sodium hydroxide solution and slowly in sodium hydrogen carbonate solution, to give red solutions which became blue on exposure to air, and was sparingly soluble after drying, in the usual solvents. An alcoholic solution gave a black ferric test. The *methyl* ester, prepared by refluxing the acid (I) (0·5 g.) for 30 minutes with methyl alcohol (25 c.c.) and concentrated sulphuric acid (2 c.c.), crystallised from acetone in dark red needles (0·45 g.), m. p. 267—268° (Found : C, 56·4; H, 3·7; MeO, 11·5. Calc. for $C_{13}H_{10}O_7$: C, 56·1; H, 3·6; MeO, 11·2%).

Decarboxylation of Purpurogallin-carboxylic Acid (with D. Caunt).—The acid (1·5 g.) was heated under reflux for 1 hour in quinoline (7·5 c.c.) with copper powder (0·75 g.). The mixture was diluted with ether (100 c.c.) and extracted with hydrochloric acid, and the ethereal layer washed, dried, and

evaporated. The residue (0·5 g.) crystallised from acetic acid in red needles, m. p. 274—276°, and was identified as purpurogallin by comparison of the phenol, the tetra-acetate, m. p. 186°, and the trimethyl ether, m. p. 176°, with authentic specimens.

*Methyl 4′-Hydroxy-2′ : 3′ : 4-trimethoxybenzo*cyclo*heptatrien-3-one-6-carboxylate.*—A suspension of purpurogallin-carboxylic acid (I) (1·0 g.) in ether (25 c.c.) was treated with excess of ethereal diazomethane, the ether removed after several hours, and the product crystallised from alcohol, giving yellow needles (0·9 g.), m. p. 156—157° (Found : C, 60·0; H, 5·1; MeO, 37·8. $C_{16}H_{16}O_7$ requires C, 60·0; H, 5·0; MeO, 38·8%). The *ester* was soluble in sodium hydroxide solution to give a yellow colour, but insoluble in sodium hydrogen carbonate solution, and gave a red colour with ferric chloride.

*4′-Hydroxy-2′ : 3′ : 4-trimethoxybenzo*cyclo*heptatrien-3-one-6-carboxylic Acid.*—The ester described above (0·2 g.) was heated on the water-bath for 30 minutes with 10% methanolic potassium hydroxide (25 c.c.). After dilution the solution was acidified and the *acid*, isolated by extraction with chloroform, crystallised from dioxan in red prisms (0·1 g.), m. p. 275—276° (Found : C, 58·7; H, 4·6; MeO, 28·7. $C_{14}H_{14}O_7$ requires C, 58·8; H, 4·6; MeO, 30·4%). The product was readily soluble in sodium hydrogen carbonate solution and gave a reddish-brown ferric test in alcoholic solution.

*4 : 2′ : 3′ : 4′-Tetramethoxybenzocyclo**heptatrien-3-one-6-carboxylic Acid and its Methyl Ester.*—Methyl 4′-hydroxy-2′ : 3′ : 4-trimethoxybenzo*cyclo*heptatrien-3-one-6-carboxylate (3·0 g.), methyl sulphate (10 c.c.), and anhydrous potassium carbonate (50 g.) in acetone (150 c.c.) were refluxed for 3 hours. The mixture was filtered, the solid was washed with acetone, and the combined filtrate and washings were evaporated to dryness, shaken with 10% sodium hydroxide solution to remove methyl sulphate, and extracted with ether. Evaporation and crystallisation of the residue from alcohol gave the methyl ester (2·3 g.) as colourless needles, m. p. 121—122° (Found : C, 61·4; H, 5·4; MeO, 43·5. Calc. for $C_{17}H_{18}O_7$: C, 61·1; H, 5·4; MeO, 46·4%). The aqueous layer was combined with the potassium carbonate residues, acidified, and extracted with ether. Evaporation and crystallisation of the residue from dioxan–light petroleum (b. p. 60—80°) gave the acid (0·6 g.) as pale yellow needles, m. p. 185—186° (Found : C, 59·8; H, 5·2; MeO, 38·1. Calc. for $C_{16}H_{16}O_7$: C, 60·0; H, 5·0; MeO, 38·8%). This acid, which was readily soluble in sodium hydrogen carbonate solution, was also formed by hydrolysis of the methyl ester, m. p. 121—122°, with methanolic potassium hydroxide.

3 : 4 : 5-Trimethoxyphthalic Anhydride.—Methyl 4′ : 2′ : 3′ : 4′-tetramethoxybenzo*cyclo*heptatrien-3-one-6-carboxylate, m. p. 121—122° (1·0 g.), in pure acetone (25 c.c.) was shaken at room temperature with 5% aqueous potassium permanganate (100 c.c.). After 2 hours the mixture was clarified with sulphur dioxide, rendered alkaline, and evaporated to dryness under reduced pressure. The residue was acidified with hydrochloric acid, then continuously extracted with ether, the extract was evaporated, and the residue distilled at 0·1 mm. Crystallisation of the distillate from absolute ether gave 3 : 4 : 5-trimethoxyphthalic anhydride (0·05 g.), m. p. 141—142°, not depressed on admixture with an authentic specimen. The *N*-methylimide crystallised from methyl alcohol in colourless needles, m. p. 127°; Manske and Holmes (*J. Amer. Chem. Soc.*, 1945, **67**, 98) give m. p. 127°.

Oxidation of Purpurogallin-carboxylic Acid with Alkaline Hydrogen Peroxide.—30% Hydrogen peroxide (40 c.c.) was added during 1 minute to a solution of purpurogallin-carboxylic acid (I) (20 g.) in sodium hydroxide (170 g.) and water (1000 c.c.) at 90°. After the intial effervescence had subsided, sodium metabisulphite (10 g.) was added, and the cooled mixture was acidified to Congo-red with 40% sulphuric acid and continuously extracted with ether for 20 hours. The extract on concentration to small bulk deposited *αβ′-dicarboxy-β-carboxymethyltropolone* (II) (7·5 g.) which crystallised from acetic acid as pale yellow needles, m. p. 230° (decomp.; rapid heating) (Found : C, 48·9; H, 3·3. $C_{11}H_8O_8$ requires C, 49·3; H, 3·0%), and gave a red ferric test in alcoholic solution.

β-Methyltropolone-β′-carboxylic Acid (III).—The above acid (II) (5·0 g.), when heated for 10 minutes at 250° in dibutyl phthalate (100 c.c.) containing a little copper powder, gave a dark solution, which was cooled, diluted with ether, and filtered. The acids were taken up in sodium hydroxide solution, recovered, and extracted several times with ethyl methyl ketone, and the solvent was removed. The residue was dissolved in dioxan (charcoal) and diluted with benzene; *β-methyltropolone-β′-carboxylic acid* (III) separated in yellow prisms (3·2 g.), m. p. 223—224°, containing solvent of crystallisation which was removed at 100°/0·1 mm. (Found : C, 59·8; H, 4·5. $C_9H_8O_4$ requires C, 60·0; H, 4·5%). The acid (III) gave a blood-red ferric test, and a crimson product with diazotised *p*-toluidine.

The acid (III) (1·0 g.) was heated to 250° with potassium hydroxide (10 g.) moistened with water, and this temperature maintained for 5 minutes. The reaction mixture was dissolved in water, then acidified, and the product isolated with ether and sublimed at 0·1 mm. Uvitic acid (0·075 g.), m. p. 290—292° not depressed on admixture with an authentic specimen (Fittig and Furtenbach, *loc. cit.*), was obtained. The methyl ester was obtained by the action of diazomethane as cream-coloured needles, m. p. 95°, undepressed by an authentic specimen.

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294. *The Electrochemistry of Boron Trifluoride Co-ordination Compounds. Part II. Boron Trifluoride–Mono(acetic Acid).*

By N. N. Greenwood, R. L. Martin, and H. J. Emeléus.

The 1 : 1 compound of boron trifluoride and acetic acid, $BF_3,CH_3{\cdot}CO_2H$, has been isolated in a highly purified state as colourless crystals melting at 37·5°. The variation of electrical conductivity with composition in the boron trifluoride–acetic acid system has been studied at 25° and a minimum in conductivity found at a composition corresponding to the compound $BF_3,CH_3{\cdot}CO_2H$. At 25·0° the conductivity of stoicheiometric boron trifluoride–mono(acetic acid) is $\kappa_{25} = 2{\cdot}16_0 \times 10^{-3}$ ohm^{-1} cm.$^{-1}$. The decomposition potential is temperature independent between 22° and 32° and has the value $D = 2{\cdot}5_0$ volt. Electrolysis at higher voltages results in the liberation of a mixture of hydrogen and boron trifluoride at the cathode, whereas the anodic gas contains oxygen, boron trifluoride, ethane, and carbon dioxide. The nature of the ions present in the molten complex is discussed and it is concluded that the compound is acetoxytrifluoroboric acid, $H(BF_2{\cdot}O{\cdot}CO{\cdot}CH_3)$.

In Part I (Greenwood, Martin, and Emeléus, *J.*, 1950, 3030) the electrochemistry of pure liquid boron trifluoride–ethyl ether was investigated. The present paper is concerned with the results of a similar investigation on boron trifluoride–mono(acetic acid), $BF_3,CH_3{\cdot}CO_2H$.

The reaction between boron trifluoride and glacial acetic acid was first studied by Landolph (*Compt. rend.*, 1877, **85**, 39; *Ber.*, 1877, **10**, 1312) who concluded, on the bases of boiling point and smell, that some acetic anhydride was formed. The first evidence for compound formation between boron trifluoride and acetic acid, however, was not reported until 50 years later, when Meerwein (*Annalen*, 1927, **455**, 227) obtained a colourless, oily, slightly-fuming liquid to which he assigned the formula $(BF_2OCOCH_3)_2H$. This compound boiled at 59°/13 mm. and was said to be comparable in acidity to sulphuric acid. Recently, Booth and D. R. Martin ("Boron Trifluoride and its Derivatives," John Wiley and Sons, 1949, p. 65) suggested that this formula was a misprint and claimed that Meerwein's data on the physical properties of the compound indicated that it was $(BF_2OCOCH_3)H$, *i.e.*, boron trifluoride–mono(acetic acid). However, Booth and D. R. Martin are themselves in error for Meerwein's data, and his subsequent statements (*Ber.*, 1933, **66**, 411; Meerwein and Pannwitz, *J. pr. Chem.*, 1934, **141**, 123), as well as the results from Nieuwland's school, show that the compound was, in fact, boron trifluoride–di(acetic acid), $BF_3,2CH_3{\cdot}CO_2H$ (Bowlus and Nieuwland, *J. Amer. Chem. Soc.*, 1931, **53**, 3835; Sowa, *ibid.*, 1938, **60**, 654).

The occurrence of a 1 : 1 compound between boron trifluoride and acetic acid was reported by Meerwein and by Meerwein and Pannwitz (*locc. cit.*) who obtained rhombic crystals, m. p. 23—24°, by passing boron trifluoride into the di-complex. These communications appear to be the only papers published on the 1 : 1 compound. In the present investigation, boron trifluoride–mono(acetic acid) was synthesised gravimetrically by passing boron trifluoride into glacial acetic acid. The compound was obtained as a solid of accurately stoicheiometric composition and m. p. 37·3°. Repeated fractional crystallisation in dry air raised the m. p. to 37·5°, after which further fractionation effected no increase. This value is considerably higher than Meerwein's value of 23—24° but is similar to Swinehart's figure of 38—39° mentioned as a private communication by Booth and D. R. Martin (*loc. cit.*). The crystals of boron trifluoride–mono(acetic acid) were extremely unstable to moist air and hydrolysed immediately, with copious fuming, to a colourless liquid. It was found that slow crystallisation of the molten compound in a thermostat at 37·1° yielded well-formed single crystals of boron trifluoride–mono(acetic acid); one such crystal was obtained as a perfect hexagonal plate of dimensions 17 × 5 × 2 mm. The crystals were colourless, transparent, and sharp-melting.

The variation of specific electrical conductivity with composition in the system boron trifluoride–acetic acid was determined at 25° and 1000 cycles A.C., in the conductivity cell shown in Fig. 1. The results are presented in Fig. 2 which incorporates the data obtained from five independent experiments.

It is seen that the conductivity passes through a maximum of $3{\cdot}17 \times 10^{-3}$ ohm^{-1} cm.$^{-1}$ at a mole ratio of ~0·24. Further addition of boron trifluoride decreases the conductivity of the

system until a minimum value of $\kappa_{25} = 1{\cdot}260 \times 10^{-3}$ ohm^{-1} cm.$^{-1}$ is reached at the mole ratio of 1·000. At this point the compound is supercooled; the conductivity of the molten stoicheiometric compound at its melting point is $\kappa_{27{\cdot}5} = 2{\cdot}19_9 \times 10^{-3}$ ohm^{-1} cm.$^{-1}$. It is only with difficulty that boron trifluoride can be absorbed beyond the stoicheiometric ratio at atmospheric pressure. A point of inflexion in the isotherm occurs at the mole ratio 0·5 (*i.e.*, $BF_3,2CH_3{\cdot}CO_2H$) for which $\kappa_{25} = 2{\cdot}13_4 \times 10^{-3}$ ohm^{-1} cm.$^{-1}$. A further inflexion occurs at about 0·8.

The D.C. current–voltage curves on supercooled boron trifluoride–mono(acetic acid) at 22·5°, 25·1°, and 32·1° all gave a well-defined decomposition potential $D = 2{\cdot}5_9$ volts. This value is just twice that observed for boron trifluoride–ethyl ether (Greenwood, Martin, and Emeléus, *loc. cit.*) and, in contrast to the values for the latter compound, is temperature independent. The gases evolved during electrolysis of the stoicheiometric compound at higher voltages were collected and analysed in an apparatus similar to that described in Part I. By means of a copper coulombmeter it was established that, for each equivalent of electricity

Fig. 1.
Conductivity–composition cell.

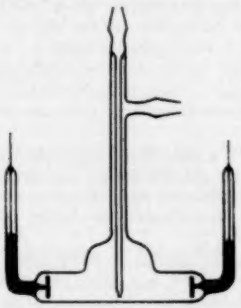


Fig. 2.
Conductivity–composition isotherm at 25·0°.

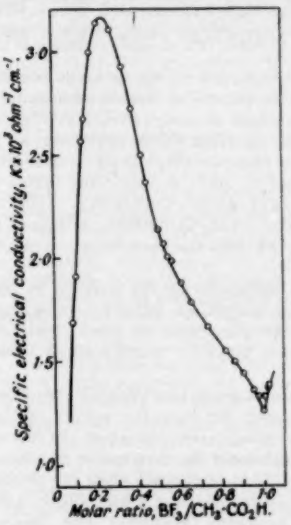
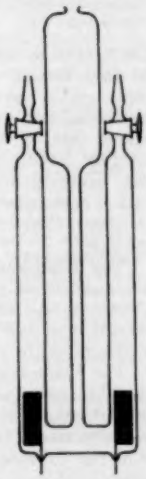


Fig. 3.
Electrolysis cell.



passed, one equivalent of hydrogen was liberated at the cathode, together with variable amounts of boron trifluoride. At the anode, a mixture of oxygen, boron trifluoride, ethane, and carbon dioxide was evolved, but this evolution was not quantitative, being extremely slow at first and accelerating as electrolysis proceeded. The observed ratios in which these gases were evolved, ethane being taken as unity, were $O_2 : BF_3 : C_2H_6 : CO_2 = 3{\cdot}4 : 1{\cdot}8 : 1{\cdot}0 : 2{\cdot}5$.

Discussion.

It was pointed out in Part I that co-ordination of an organic molecule to boron trifluoride involves an electron displacement which confers on the complex a much higher degree of ionisation than exists in either the donor or the acceptor molecule alone. This enhanced ionisation is reflected in the large increase in electrical conductivity which accompanies co-ordination. In the present instance, the specific conductivity of glacial acetic acid, $\kappa_{25} = 1{\cdot}12 \times 10^{-9}$ ohm^{-1} cm.$^{-1}$ (Rabinowitsch, *Z. physikal. Chem.*, 1926, **119**, 59), is raised to $1{\cdot}26 \times 10^{-6}$ ohm^{-1} cm.$^{-1}$ by co-ordination to an equimolar proportion of boron trifluoride.

The variation of conductivity with composition in the boron trifluoride–acetic acid system indicates that compound formation occurs at 1 : 1 and possibly also 1 : 2 proportions. The minimum in conductivity observed at the molar ratio 1·000 is strong evidence for the existence

of the compound $BF_3,CH_3{\cdot}CO_2H$. Such evidence is desirable to confirm Meerwein's deduction of compound formation from the results of analyses, particularly as he showed that the liquid could not be distilled without change in composition. The conductivity minimum in conjunction with the m. p. maximum at 37·5° provides an unequivocal demonstration of the existence of boron trifluoride–mono(acetic acid) as a stoicheiometric compound. The existence of boron trifluoride–di(acetic acid) is already well established by the work of Meerwein and of Nieuwland (*locc. cit.*) and a detailed discussion of its properties falls outside the scope of the present paper. It may be mentioned, however, that the absence of a minimum at the ratio 0·500 is not inconsistent with the formation of the 1 : 2 compound, for the work of Bloom and Heymann (*Proc. Roy. Soc.*, 1947, *A*, **188**, 392) has demonstrated that inflexion in a conductivity isotherm may well resolve into a minimum at sufficiently low temperatures.

The possible modes of ionic dissociation in the highly conducting compound boron trifluoride–mono(acetic acid) may be written in the following ways, depending on whether dissociation involves rupture of the carbon–oxygen, carbon–hydrogen, or oxygen–hydrogen bond:

$$BF_3,CH_3{\cdot}CO_2H \longrightarrow CH_3{\cdot}CO^+ + BF_3,OH^- \quad (1)$$

$$BF_3,CH_3{\cdot}CO_2H \longrightarrow H^+ + BF_3,CH_2{\cdot}CO_2H^- \quad (2)$$

$$BF_3,CH_3{\cdot}CO_2H \longrightarrow H^+ + BF_3,CH_3{\cdot}CO_2^- \quad (3)$$

Electrolysis at 100—105 volts results in the cathodic liberation of one equivalent of hydrogen for each faraday of electricity passed so that mechanism (1) is definitely eliminated, and the compound is not to be considered as acetyl hydroxytrifluoroborate, $CH_3{\cdot}CO[BF_2{\cdot}OH]$. Of the remaining two mechanisms, equation (3) is preferred, as it involves dissociation at a point nearer that of the primary electron displacement induced by the formation of the donor–acceptor bond. In this way it may be seen that boron trifluoride–mono(acetic acid) is, in fact, acetoxytrifluoroboric acid, $H[BF_2{\cdot}O{\cdot}CO{\cdot}CH_3]$. This compound should not be confused with "acetoxyboron fluoride," $(CH_3{\cdot}CO{\cdot}O{\cdot}BF)_2$, obtained by Kroeger, Sowa, and Nieuwland (*J. Amer. Chem. Soc.*, 1937, **59**, 965) by acetylation of dihydroxydifluoroboric acid with acetyl chloride.

The evolution of boron trifluoride at the cathode is presumably a secondary reaction, as the amount of gas evolved varied in different experiments. The possibility of catalytic reduction to a less stable complex such as boron trifluoride–acetaldehyde with consequent liberation of boron trifluoride must be eliminated in view of the quantitative evolution of hydrogen at the cathode.

The anode reactions are of a more complicated character, but it is possible to formulate a plausible mechanism to account for both the nature of the gases evolved and their relative proportions. The somewhat speculative nature of the following considerations, however, in no way detracts from the fundamental demonstration of the mode of dissociation as determined from the cathode analysis. It is suggested that the primary anodic discharge gives rise to acetoxytrifluoroborate radicals which have a long life in acetoxytrifluoroboric acid on account of regeneration by solvent exchange (Waters, "The Chemistry of Free Radicals," Clarendon Press, 1946, p. 19).

$$BF_3,CH_3{\cdot}CO_2^- \longrightarrow BF_3,CH_3{\cdot}CO_2 + e^-$$

$$BF_3,CH_3{\cdot}CO_2 + HO{\cdot}CO{\cdot}CH_2,BF_3 \longrightarrow BF_3,CH_3{\cdot}CO_2H + O{\cdot}CO{\cdot}CH_2,BF_3$$

These radicals may dimerise to the boron trifluoride complex of diacetyl peroxide in preference to immediate decomposition, and this would account for both the slow initial evolution of gas at the anode and the fact that the evolution of gaseous products at this electrode is not quantitative. Such behaviour is paralleled by the well-known stability of acetate radicals and of diacetyl peroxide in glacial acetic acid at temperatures similar to those used in the present experiments (*ca.* 30°) (Waters, *loc. cit.*; Kharasch and Gladstone, *J. Amer. Chem. Soc.*, 1943, **65**, 15). As the electrolysis proceeds, decomposition of the peroxide complex will occur in two ways. Complete disruption may take place in accord with the classical experiments of Kolbe, to give boron trifluoride, ethane, and carbon dioxide:

$$(BF_3,CH_3{\cdot}CO_2)_2 \longrightarrow 2BF_3 + C_2H_6 + 2CO_2$$

Alternatively disproportionation of the peroxide compound may give oxygen and the boron trifluoride complex of acetic anhydride. It is difficult to construct an equation for this reaction as the constitution of the latter compound is still a matter of some doubt (cf. Bowlus and

Nieuwland, *loc. cit.*; Morgan and Taylor, *J. Soc. Chem. Ind.*, 1931, **50**, 869; Meerwein, *loc. cit.*; Meerwein and Vossen, *J. pr. Chem.*, 1934, **141**, 149). The discussion shows, however, that the observed anodic gases may well be evolved by discharge of the anion of acetoxytrifluoroboric acid.

The variation of the electrical conductivity, viscosity, and density of boron trifluoride–mono(acetic acid) as a function of temperature forms the subject of a subsequent paper.

Experimental.

Boron Trifluoride.—The gas used was a pure-grade material supplied by courtesy of the Imperial Smelting Company. The purity was checked tensimetrically and by molecular-weight determination. The vapour pressure was measured in the range −133° to −112° by use of a calibrated ethylene thermometer, and the results agreed with the data of Pohland and Harlos (*Z. anorg. Chem.*, 1932, **207**, 242). The molecular weight of the gas was 67·6 (Calc. for BF_3: *M*, 67·8).

Boron Trifluoride–Mono(acetic Acid).—This compound was prepared gravimetrically to 1 part in 2000 by passing boron trifluoride through "AnalaR" glacial acetic acid contained in an all-glass water-cooled reaction vessel. The bubble rate was controlled by means of a subsidiary valve inserted in the copper lead from the storage cylinder, and a copper-to-glass ground joint from the valve to the reaction vessel prevented access of water vapour during the preparation. The complex crystallised completely at room temperature leaving no mother-liquor (cf. Meerwein and Pannwitz, *loc. cit.*), and the melting point, as determined by the cooling curve procedure, was 37·3°. Further purification of the compound was effected by fractional crystallisation in a sealed vessel in the presence of dry air. The compound was melted at 39° and, when slowly recrystallised at 37·1°, gave well-formed single crystals in the form of colourless, transparent, hexagonal plates. After 5 recrystallisations the m. p. had risen to 37·5° and subsequent fractionation effected no further increase. The temperature was measured with a calibrated thermometer graduated in tenths of a degree.

Carbon and hydrogen micro-analyses confirmed the identity of the recrystallised compound (Found: C, 18·5; H, 3·24. Calc. for $BF_3,CH_3{\cdot}CO_2H$: C, 18·8; H, 3·13%).

Conductivity of the Boron Trifluoride–Acetic Acid System.—The design of the cell used to determine the variation of electrical conductivity with composition of the boron trifluoride–acetic acid system is shown in Fig. 1. The cell was of the conventional type in soda glass, with platinum electrodes, but modified by the addition of an internally sealed tube by means of which boron trifluoride could be led into the system. The cell was enlarged above the plane of the electrodes to accommodate the increase in volume which accompanies complex formation. Mixtures of the desired composition were thus prepared *in situ* and their conductivities at 1000 cycles A.C. measured using the Wheatstone-type network described in Part I. The inlet and outlet tubes were provided with ground glass stoppers to minimise access of moisture. Platinum leads were sealed into the side-arms of the cell to prevent evaporation of mercury with consequent change in weight of the cell. The volume of liquid required was ~6 ml. and the cell constant was 1·857 $cm.^{-1}$. Thermostatic control was obtained to $\pm 0{\cdot}05°$ by using the apparatus described in Part I. To reduce losses resulting from evaporation of the acetic acid, and to guard against thermal decomposition of the compound, the conductivity–composition experiments were carried out at 25°. It was found unnecessary to supercool to lower temperatures.

D.C. Measurements.—The current–voltage curves for different samples were determined by using a standard circuit which incorporated a microammeter and voltmeter. At 22·5°, 25·1°, and 32·1° well-defined decomposition potentials were obtained, the value in each case being 2·50 v. The first visible evolution of gas was at the cathode at an applied potential of 4 v.; no gas appeared at the anode. At much higher potential differences, of the order of 100 v., there was copious evolution of cathodic gas; the anodic evolution was slow initially but after the electrolysis had proceeded for some time the rate increased and eventually exceeded that at the cathode.

Identification of Cathode Gases.—The apparatus used for generation and identification of the gaseous products of electrolysis was similar to that described in Part I. About 150 ml. of boron trifluoride–mono(acetic acid) were electrolysed at ~100 v. in the cell sketched in Fig. 3. A copper coulombmeter of standard design was inserted in series with the cell. The gas evolved under these conditions was led into the vacuum system and passed through a trap which was kept immersed in liquid oxygen. The number of moles of non-condensable gas was calculated from the pressure in a constant-volume manometer. In successive experiments on different samples, 3·0 and 4·1 millifaradays liberated 1·5 and 2·1 millimoles of non-condensable gas. Experimental determinations of the molecular weight of the gas gave 2·9 and 2·0 respectively. The gas was sparked with air in a Hempel apparatus and confirmed as hydrogen.

The fraction condensable in liquid oxygen weighed 40·2 mg. and 134·6 mg. respectively in the two experiments. Molecular-weight determinations gave 66·7 and 66·0 (Calc. for BF_3: 67·8). The vapour pressure of this fraction, measured manometrically between −133° and −114°, corresponded with Pohland and Harlos's data (*loc. cit.*) for boron trifluoride.

Identification of Anode Gases.—In the first electrolysis experiment only ~3 ml. of anode gas were evolved in the first hour compared with 50 ml. at the cathode. The gas amounted to 0·1 millimole and was not condensable in liquid oxygen. This quantity was too small for molecular-weight and Hempel analysis to be carried out. The second experiment followed the course of the first, but the anodic evolution rapidly increased during the second hour and ~50 ml. of gas were collected. This was fractionated by passage through a trap immersed in liquid oxygen. The non-condensable fraction (0·75 millimole) had a molecular weight of 32·9, and its absorption by alkaline pyrogallol confirmed its identity as oxygen.

The fraction condensable in liquid oxygen weighed 58·6 mg. and had a molecular weight of 51·7 (Calc. for the mixture $2BF_3 + C_2H_6 + 2CO_2$: 50·7). The b. p.s of these constituents were too close to permit quantitative vacuum-fractionation of the mixture, but their separation was accomplished by chemical means. The gas was condensed into a reaction bulb and shaken with distilled water until absorption was complete. The residual gas was distilled through a trap at the temperature of melting alcohol, −112°, into the molecular-weight bulb and weighed. In this way boron trifluoride was removed in the form of its hydrate. Carbon dioxide was then estimated by absorption in 10% aqueous sodium hydroxide. The residual gas weighed 6·7 mg. and a molecular-weight determination on this small quantity gave a value ~34 (Calc. for ethane: 30). The identity of the gas was confirmed by explosion in a Hempel pipette. The analysis therefore indicates that the condensable gas liberated at the anode under the present conditions of electrolysis are:

Constituent.	Weight, mg.	Mole ratio. Exptl.	Calc.
Boron trifluoride	27·2	1·8	2
Carbon dioxide	24·7	2·5	2
Ethane	6·7	1·0	1
Total	58·6		
Wt. of anode gas taken	58·6 mg.		

The amount absorbed in water and alkali totalled 51·9 mg. (calc., 51·7 mg.); this suggests that the hydrate of boron trifluoride decomposes slightly under high vacuum, thereby rendering the boron trifluoride figure low and that for carbon dioxide high.

Two of the authors (N. N. G. and R. L. M.) thank the Commissioners of the Exhibition of 1851 for the award of Overseas Studentships during the tenure of which this work was carried out.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, February 5th*, 1951.]

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295. *The Infra-red Spectra and Chemical Structure of Some Aromatic Disulphides, Disulphones, and Thiolsulphonates.**

By J. CYMERMAN and J. B. WILLIS.

The infra-red spectra of a number of aromatic disulphides, disulphones, and thiolsulphonates are reported, and the characteristic absorption bands for the S–O, C–S, and S–S linkages are discussed. Our interpretation of the infra-red spectra confirms the chemical evidence that the compounds hitherto known as "disulphoxides" have the structure R·SO_2·S·R′ rather than R·SO·SO·R′ and should therefore be referred to as thiolsulphonates.

ALTHOUGH thiolsulphonates ("disulphoxides") * have been known for over eighty years (cf. Marcker, *Annalen*, 1865, **136**, 83; Otto, *ibid.*, 1868, **145**, 13, 317) and their reactions have received considerable study, their structures have not yet been unequivocally established by physico-chemical evidence.

The symmetrical disulphoxide structure (I) was favoured by Fromm and Palma (*Ber.*, 1906, **39**, 3308), Hinsberg (*Ber.*, 1908, **41**, 2836, 4294; 1909, **42**, 1278), Gutmann (*ibid.*, 1908, **41**, 3351; cf. also Toennies and Lavine, *J. Biol. Chem.*, 1936, **113**, 571, 583). These compounds have also been considered as mixed anhydrides (II) (Gilman, "Organic Chemistry," p. 912, John Wiley & Sons, New York, 1943) and latterly as thiolsulphonates (III) (Smiles and Gibson, *J.*, 1924, 176; Gibson, Miller, and Smiles, *J.*, 1925, 1821; Miller and Smiles, *J.*, 1925, 224; Gilman, Smith, and Parker, *J. Amer. Chem. Soc.*, 1925, **47**, 851), while optical measurements (Hilditch, *J.*, 1910, 1091) appeared to show that either the disulphoxide or the thiolsulphonate structure could exist, according to the similar or dissimilar nature of R and R′.

R—SO—SO—R′	R—SO—O—S—R′	R—SO_2—S—R′
(I.)	(II.)	(III.)

In this paper we consider the infra-red spectroscopic evidence obtained from the study of a series of these compounds. No previous measurements on infra-red absorption of thiolsulphonates have been found in the literature, and there is little information on the related disulphides and disulphones. A series of these compounds has therefore been prepared and their infra-red spectra have been examined.

* In this paper the systematic name "thiolsulphonate" is used throughout, as our work shows this to be the correct structure of these compounds.

Experimental.

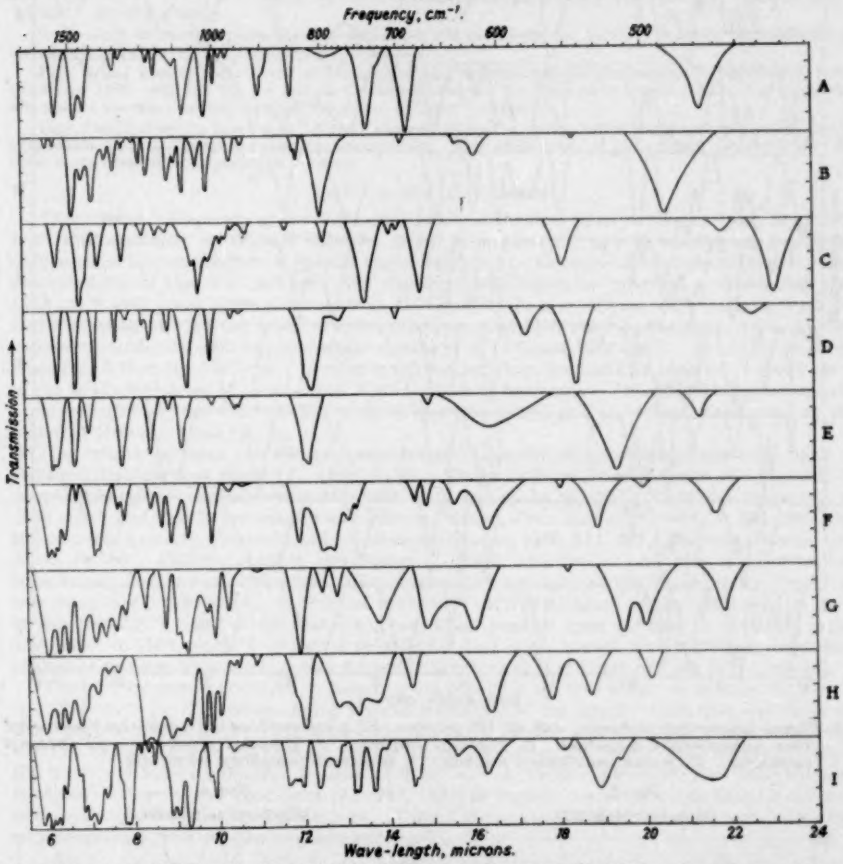
Source of Materials.—Diphenyl sulphoxide was prepared according to Hinsberg (*Ber.*, 1910, **43**, 289) and had m. p. 69·5—70°, b. p. 114—116°/0·02 mm.

Diphenyl sulphone (Beckurts and Otto, *Ber.*, 1878, **11**, 2066) had m. p. 123—124°.

Diphenyl, di-*p*-tolyl, and di-*o*-tolyl disulphide had m. p. 61°, 47—48°, and 38° respectively.

Di-*p*-cyanophenyl and di-*p*-aminophenyl disulphide were pure samples prepared by Bauer and Cymerman (*J.*, 1949, 3434). The preparation and physical constants of di-*p*-carbamylphenyl disulphide,

Fig. 1.



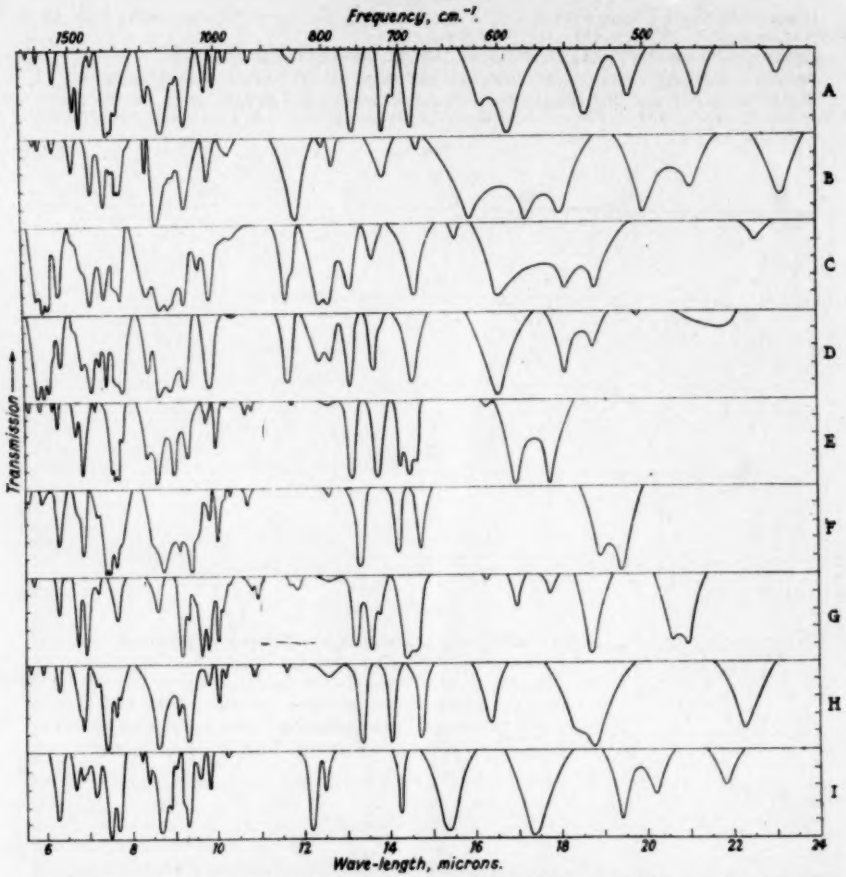
A, Diphenyl disulphide. B, Di-p-tolyl disulphide. C, Di-o-tolyl disulphide. D, Di-p-cyanophenyl disulphide. E, Di-p-aminophenyl disulphide. F, Di-p-carbamylphenyl disulphide. Di-p-amidinophenyl disulphide (G) dihydrochloride, (H) dibenzenesulphonate. I, Diphenyl disulphide 4 : 4′-di-(carboxyimino ethyl ether) dihydrochloride.

diphenyl disulphide 4 : 4′-di(carboxyimino ethyl ether) dihydrochloride, and di-*p*-amidinophenyl disulphide dihydrochloride and dibenzenesulphonate have been given in a previous publication (Bauer and Cymerman, *J.*, 1950, 109).

Phenyl benzenethiolsulphonate (Hinsberg, *Ber.*, 1908, **41**, 2838) had constant m. p. 45°.

p-Cyanophenyl *p*-cyanobenzenethiolsulphonate (Cymerman, Koebner, and Short, *J.*, 1948, 381), *p*-carbamylphenyl *p*-carbamylbenzenethiolsulphonate, and phenyl benzenethiolsulphonate 4 : 4′-di-(carboxyimino ethyl ether) dihydrochloride (Bauer and Cymerman, *loc. cit.*) were the pure samples described.

FIG. 2.



A, Phenyl benzenethiolsulphonate, and its (B) p-cyano-, (C) p-carbamyl, and (D) p-(carboxyimino ethyl ether hydrochloride) derivatives. E, Diphenyl sulphone. F, Diphenyl disulphone. G, Diphenyl sulphoxide. H, Bisbenzenesulphonyl sulphide. I, Bistoluene-p-sulphonyl trisulphide.

FIG. 3.

Diphenyl sulphoxide.

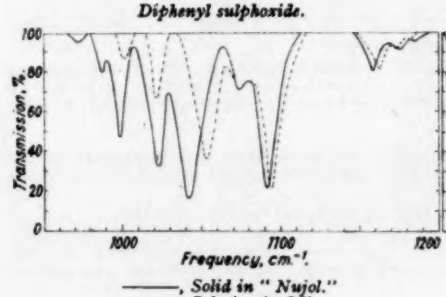
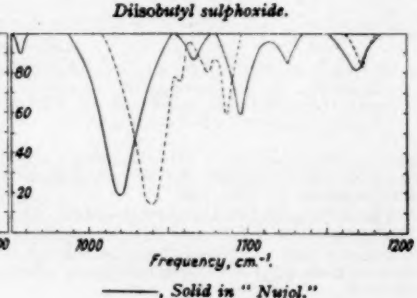


FIG. 4.

Diisobutyl sulphoxide.



———, *Solid in "Nujol."*
– – – –, *Solution in* CCl_4.

———, *Solid in "Nujol."*
– – – –, *Solution in* CCl_4.

Specimens of diphenyl disulphone, bisbenzenesulphonyl sulphide, and bistoluene-*p*-sulphonyl trisulphide were kindly supplied by Dr. A. McL. Mathieson, and di*iso*butyl sulphoxide by Professor W. Davies.

Spectroscopic Technique.—The infra-red spectra from 2·5 to 25 μ. (4000—400 cm.$^{-1}$) were measured with a Perkin–Elmer Spectrometer, Model 12B, using rock-salt optics for the region 4000—670 cm.$^{-1}$ and potassium bromide for the region 670—400 cm.$^{-1}$.

The specimens were measured in suspension in "Nujol" or methylene iodide–sulphur. In the 400—700-cm.$^{-1}$ range "Nujol" has practically no absorption in the thickness required for work with suspensions, while methylene iodide has an intense band at 570 cm.$^{-1}$ and a weaker one at about 490 cm.$^{-1}$. Methylene iodide, however, is transparent in the 1350 and 1450 cm.$^{-1}$ regions where "Nujol" absorbs heavily.

Some work on monosulphoxides was carried out with solutions in "AnalaR" carbon tetrachloride in a rock-salt cell of fixed path-length (about 0·5 mm.).

Figs. 1 and 2 show the spectra of disulphides and oxygen-containing compounds respectively over the range 1800—420 cm.$^{-1}$; the sample thickness used for the long-wave-length region, however, was not always the same as that used for the 4000—670-cm.$^{-1}$ region.

Figs. 3 and 4 show the spectra, in "Nujol" suspension and in carbon tetrachloride solution, of diphenyl sulphoxide and di*iso*butyl sulphoxide respectively. The absorption of the carbon tetrachloride has been subtracted for the spectra in solution.

Results and Discussion.

Characteristic Frequency of the Sulphoxide Link.—Schreiber (*Analyt. Chem.*, 1949, **21**, 1168), from measurements on thionyl chloride, diphenyl sulphoxide, and di-*n*-butyl sulphoxide in carbon tetrachloride solution, suggested tentatively that an absorption band near 1190 cm.$^{-1}$ was characteristic of the S–O linkage. For diphenyl sulphoxide he reported a strong band at 1183 cm.$^{-1}$ with a well-defined shoulder at 1166 cm.$^{-1}$. In a repetition of Schreiber's work we found no peak at 1183 cm.$^{-1}$ but a well-marked band at 1160 cm.$^{-1}$ in the solid (1163 cm.$^{-1}$ in carbon tetrachloride solution) with slight shoulders at 1173 and 1183 cm.$^{-1}$. It will be observed from Fig. 3 that the 1163-cm.$^{-1}$ band is much weaker than the band at 1053 cm.$^{-1}$ (1042 cm.$^{-1}$ in the solid), which we have reason to think is the S–O frequency. Di*iso*butyl sulphoxide gave a strong band at 1019 cm.$^{-1}$ (solid) or 1039 cm.$^{-1}$ (solution) and only weak absorption in the region of 1190 cm.$^{-1}$ (see Fig. 4).

Our results on these two monosulphoxides are, however, in good agreement with those of Barnard, Fabian, and Koch (*J.*, 1949, 2442). These authors, from a study of a number of monosulphoxides, concluded that the S–O band has a characteristic vibration frequency of 1055 cm.$^{-1}$, and that in accordance with theory (Moffitt, *Proc. Roy. Soc.*, 1950, *A*, **200**, 409) and experiment (Amstutz, Chessick, and Hunsberger, *Science*, 1950, **111**, 305; Barnard, Fabian, and Koch, *loc. cit.*; Phillips, Hunter, and Sutton, *J.*, 1945, 146) the S–O bond in sulphoxides has considerable double-bond character. The oxygen atom can take part in intermolecular bonding, which explains the shift of 11 cm.$^{-1}$ in the 1053-cm.$^{-1}$ band of diphenyl sulphoxide and of 20 cm.$^{-1}$ in the 1039-cm.$^{-1}$ band of di*iso*butyl sulphoxide on passage from solution to the solid state. The band at 1163 cm.$^{-1}$ in diphenyl sulphoxide does not undergo an appreciable frequency change on passage from solution to solid, which confirms that it is not due to a S–O vibration.

The high frequency (1238 cm.$^{-1}$) found by Schreiber for the S–O vibration in thionyl chloride (cf. 1229 cm.$^{-1}$ for the corresponding Raman frequency of the liquid: Cabannes and Rousset, *Ann. physique*, 1933, **19**, 229) is explained by Barnard, Fabian, and Koch (*loc. cit.*) by supposing that, on replacement of the organic substituents by halogen, the contribution of the structure $RR'S^+–O^-$ is lowered relative to that of $RR'S{=}O$. A similar argument has been used by Hartwell, Richards, and Thompson (*J.*, 1948, 1436) to explain the increased carbonyl frequency in halogen-substituted acids and ketones. Table I shows the C=O and S=O frequencies for some related carbonyl and sulphoxy-compounds.

Table I.

Molecule.	Frequency (cm.$^{-1}$).	Molecule.	Frequency (cm.$^{-1}$).
$(CH_3)_2C{:}O$ [1] (*l*)	1718	$R_1R_2S{:}O$ [4] (*s*)	1040
$(CH_3O)_2C{:}O$ [2] (*l*)	1747	$(CH_3O)_2S{:}O$ [5] (*l*)	1200
$(C_2H_5O)C{:}O$ [3] (*l*)	1744	$(C_2H_5O)_2S{:}O$ [5] (*l*)	1200
$Cl_2C{:}O$ [5] (*l*)	1807	$Cl_2S{:}O$ [6] (*l*)	1229

[1] Hartwell, Richards and Thompson, *loc. cit.* [2] Dadieu and Kohlrausch, *Wien. Ber.*, 1930, **139**, 77. [3] Ananthakrishnan, *Proc. Indian Acad. Sci.*, 1937, **5***A*, 285. [4] Barnard, Fabian, and Koch, *loc. cit.* [5] Matossi and Aderhold, *Z. Physik*, 1931, **68**, 683. [6] Cabannes and Rousset, *loc. cit.*

The Structure of the So-called "Disulphoxides."—If these compounds had the formula (I) or (II), sulphur–oxygen vibrations in the neighbourhood of 1040 cm.$^{-1}$ would be expected. In (I) there would be an S–O bond from each of the two adjacent sulphur atoms, and some slight

vibrational interaction might be expected, as in the case of adjacent C:O bonds. The Raman spectra of 1 : 2-diketones recorded by Kohlrausch and Pongratz (*Ber.*, 1934, **67**, 976) show that a shift of only 5—15 cm.$^{-1}$ occurs in benzil (1683 cm.$^{-1}$, compared with 1678 cm.$^{-1}$ for dibenzoylmethane) and in diacetyl (1725 cm.$^{-1}$, compared with 1710 cm.$^{-1}$ for 3 : 3-dimethylpentane-2 : 4-dione); and Thompson (*Trans. Faraday Soc.*, 1940, **36**, 988) records 1730 cm.$^{-1}$ for glyoxal, compared with 1745 cm.$^{-1}$ for formaldehyde. Although, as pointed out by Barnard, Fabian, and Koch, the analogy between the sulphoxide group and the carbonyl group is not perfect on account of the different geometry of the sulphur and carbon valencies, it is unlikely that interaction would shift the S–O frequencies by more than about 10 cm.$^{-1}$ from the mean position. Now the thiolsulphonates have no characteristic bands in the neighbourhood of 1040 cm.$^{-1}$. The nearest bands to this frequency are those at 1020 and 1080 cm.$^{-1}$, which cannot be due to an S–O vibration as they occur with all the disulphides as well as with the thiolsulphonates. There are, however, *two* strong bands, at about 1150 and 1340 cm.$^{-1}$, at almost the same frequency as in sulphur dioxide (ν_1 = 1151 cm.$^{-1}$, ν_3 = 1361 cm.$^{-1}$) and the sulphones (Schreiber, *loc. cit.*). Table II shows these frequencies for the thiolsulphonates and disulphones studied in the present work. The inference is that the compounds hitherto known as "disulphoxides" have the structure R·SO_2·S·R′ rather than R·SO·SO·R′ and should therefore be referred to as thiolsulphonates.

TABLE II.

Thiolsulphonates, R·SO_2·SR, R =	ν_1.	ν_3.	Sulphones,	ν_1.	ν_3.
Ph	1144	1331	Ph_2SO_2	1158	1298, 1312, 1319
p-C_6H_4·CN	1154	1342	$(Ph·SO_2)_2$	1150	1339, 1354
p-C_6H_4·CO·NH_2	1154	1342	$(Ph·SO_2)_2S$	1166	1345, 1361
p-C_6H_4·C(OEt):NH,HCl	1154	1341	$(p\text{-}C_6H_4·SO_2·S)_2S$	1154	1338

TABLE III.

Compound.	C–S band, cm.$^{-1}$.	Aromatic "non-para" band, cm.$^{-1}$.	S–S band, cm.$^{-1}$.
Disulphides, R_2S_2, R =			
Ph	689	737 (?)	468
p-C_6H_4Me	696	—	486
o-C_6H_4Me	676	702 (w)	433
p-C_6H_4·CN	580 or 705 (w)	—	443
p-C_6H_4·NH_2	612 or 670 (w)	—	469
p-C_6H_4·CO·NH_2	673 and/or 686	—	461
p-C_6H_4·C(NH_2):NH,HCl	674	—	457
p-C_6H_4·C(NH_2):NH (dibenzenesulphonate)	690	—	497
p-C_6H_4·C(OEt):NH,HCl	685 and/or 690	—	465
Thiolsulphonates, R·SO_2·SR, R=			
Ph	686	706	470
p-C_6H_4·CN	631 and/or 680	—	473
p-C_6H_4·CO·NH_2	683	—	463
p-C_6H_4·C(OEt):NH,HCl	687	—	461
Miscellaneous Sulphur-containing Aromatic Compounds:			
Diphenyl sulphone	683, 690	699	—
Diphenyl disulphone	680	705	?
Diphenyl sulphoxide	686	695	—
Bis(benzenesulphonyl) sulphide	681	715	449
Bis(toluene-*p*-sulphonyl) trisulphide	653 and/or 702	—	458
Aliphatic Compounds:			
Methionine	688	—	—
Cysteine hydrochloride	651	—	—
Cystine	674	—	454
Glutathione	691	—	—

It will be seen that in the solid state, the higher frequency of the sulphones is often split.

No band characteristic of the SO_2 deformation frequency (519 cm.$^{-1}$ in sulphur dioxide itself) was recognisable in the spectra.

Carbon–Sulphur Vibration Frequencies.—The assignment of characteristic vibration frequencies to the C–S bonds in molecules as complex as the present ones is rather uncertain. Trotter and Thompson (*J.*, 1946, 481) and also Sheppard (*Trans. Faraday Soc.*, 1950, **46**, 429) concluded from the study of a number of simple aliphatic sulphides and disulphides that the

C–S frequency was variable but usually lay between 600 and 700 cm.$^{-1}$. All the compounds studied in the present investigation showed bands in this region. An unambiguous assignment is not possible, however, as the ν_4 frequency of the benzene ring, which appears in benzene itself as a strong band at 671 cm.$^{-1}$, persists in a large number of monosubstituted, but not in *p*-disubstituted, benzene derivatives, as a band near 700 cm.$^{-1}$. This has been noted by other authors (Barnes *et al.*, *Analyt. Chem.*, 1948, **20**, 402). Table III shows a possible assignment, and includes also some aliphatic sulphur compounds for comparison. The S–S frequencies are discussed below.

Sulphur–Sulphur Vibration Frequencies.—All the disulphides, thiolsulphonates, and disulphones, with the exception of diphenyl disulphone, show a band in the region 430—490 cm.$^{-1}$ (see Table III). The band is frequently weak or badly defined, but may be due to an S–S vibration. Trotter and Thompson, and also Sheppard (*loc. cit.*), identified such bands in the 450—520-cm.$^{-1}$ region for several simple aliphatic disulphides; in general the bands were found to be weak in absorption but strong in Raman spectra.

It is possible that the failure of diphenyl disulphone to give a band in this region is caused by the molecule's possessing a centre of symmetry and existing in the *trans*-form only, so that the S–S vibration is inactive in absorption. In the solid state the selection rules would not be expected to apply rigorously, but the band due to the S–S vibration should be weak if the molecule has a centre of symmetry. It is known from the *X*-ray structure analysis of Dawson, Mathieson, and Robertson (*J.*, 1948, 322) that the space group is either $P1$ or $P\bar{1}$. In the latter case the molecule has a centre of symmetry.

The aliphatic disulphide, cystine, was found to have a band at 454 cm.$^{-1}$ which can be attributed to an S–S vibration.

We acknowledge with gratitude much helpful discussion with Professor R. J. W. LeFèvre, Dr. A. L. G. Rees, and Mr. A. Walsh, and thank Messrs. L. Bauer and W. J. Sheldon for valuable assistance.

(J. C.) Chemistry Department, University of Sydney.
(J. B. W.) Division of Industrial Chemistry,
Commonwealth Scientific and Industrial Research Organization,
Melbourne. [*Received, November 6th*, 1950.]

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296. *Lanthanon Purifications by the Use of Hexa-antipyrine Lanthanon Iodides.*

By J. K. Marsh.

Fractional crystallisation of heavy hexa-antipyrine lanthanon iodide $[Ln(C_{11}H_{12}ON_2)_4]I_3$ yields efficiently pure lutetium material. The separation of thulium and lutetium is good, and that of thulium from erbium and yttrium very satisfactory though more difficult. Yttrium separates very slowly from erbium, and, uniquely, on the thulium side. Yttrium separates well from holmium, but holmium, dysprosium, and terbium are not efficiently separated. No separation of neodymium and praseodymium was observed.

The good initial separation of lutetium from neighbouring earths obtained by a fractional precipitation of an iodide solution with antipyrine, followed by ten series of crystallisations of the resulting hexa-antipyrine lutetium iodide, has already been recorded (*J.*, 1950, 577). This work has now been extended, and the purification of both lutetium and thulium achieved with a satisfactory economy of effort. When the starting material is already spread into four or five fractions, less than 3000 crystallisations, and withdrawal of ytterbium by means of sodium amalgam, yields 99·9%-pure Lu_2O_3 33%, 99%-pure Tm_2O_3 11%, pure Yb_2O_3 2%, $(Lu,Tm)_2O_3$ intermediates 13%, $(Tm,Y,Er)_2O_3$ 9%, $(Y,Er)_2O_3$ 32%. The bulk of the originally associated erbium had been previously freed from thulium by 3000 bromate crystallisations, and the greater part of the ytterbium withdrawn by means of sodium amalgam. In view of the slight incompleteness of the withdrawal of ytterbium previously encountered by the author (*J.*, 1943, 8), it was considered inadvisable to attempt its final removal before further concentration by the antipyrine fractionation. However, an improved technique has demonstrated the possibility of withdrawal to below the limits of spectroscopic detection, so that it now becomes advisable to make this complete withdrawal before the antipyrine fractionation.

The surprising occurrence of yttrium between thulium and erbium also points to the desirability of eliminating all yttrium from the material by ferricyanide fractionation (Marsh, *J.*, 1947, 118) or by a process using ethylenediaminetetra-acetic acid.

Another fractionation series consisting of yttrium, holmium, dysprosium, and small amounts of terbium and gadolinium was studied. After 50 series (1500 crystallisations) a considerable amount of yttrium had been eliminated at the head, but progress in separating dysprosium and holmium was considered insufficient to indicate superiority of this mode of fractionation over other known methods. The fractionation is easy and safe, but the dimethyl phosphates are more efficient though much harder to crystallise. The separation of dysprosium and terbium is rather similar and not very satisfactory by either method. Traces of terbium tinted the oxides from most of the iodide fractions, though only a small amount of oxides from the tail was deeply coloured by it. Solutions in course of fractionation contain the equivalent of about 15 g. of oxide per l. in the antipyrine process, 40—50 as dimethyl phosphates, and over 500 as bromates. The advantage of the bromate method for large quantities is obvious even if a much larger number of crystallisations is required.

Only for lutetium and thulium is it likely that the antipyrine iodide salt possesses any advantage over known methods of purification, but for these two metals there is a clear case for its employment after they have had suitable preliminary concentration.

It is believed that the collection of yttrium between erbium and thulium here experienced has not previously been observed. The author has previously discussed the wandering of the position of yttrium through the lanthanon group (*J.*, 1947, 118, 1084) and pointed out that the electron density of yttrium is lower than that of the lanthanons and may permit of a relatively greater increase in size in passing from an ionic to a covalent state. However, the behaviour of yttrium is very erratic and does not follow a simple ionic–covalent transition. Owing to its lower atomic number the ion itself will be more compressible than lanthanon ions, and crystal structure considerations will introduce a constitutive factor not yet predictable, which may account for the variations. It is perhaps significant that the six antipyrine groups (156 atoms) are probably the largest and heaviest assemblage known to co-ordinate with the positive ions of these elements. As a result we may postulate a cramping effect upon the ions. An unusually small size of the yttrium ion would result from its higher compressibility where in general a compressive force is operative on the positive ions of a series of salts.

It has been noticed repeatedly that, especially on first setting up an iodide antipyrine series, a very insoluble product collects at the head in very small crystals of the usual type, but on further crystallisation these may suddenly change to long silky needles. It is thought that this may indicate a separation of isomeric forms of antipyrine, the insoluble needles being most probably associated with a concentration of *trans*-molecules. Antipyrine supplied from three or four different sources all showed the same phenomenon. It is known that antipyrine reacts at times according to more than one constitutional formula. On account of this phenomenon it is probably impossible to determine accurately the solubilities of the antipyrine salts of the series. Although the crystals present ten faces resembling a cubo-octahedron, as already reported, a crystallographic examination by Mr. H. M. Powell showed them to be in fact trigonal. After long boiling of solutions the habit is different, growth being in stout needles formed from a series of telescoped crystals. After long crystallisation, solutions tended to become slightly alkaline at the head and acid at the tail.

Experimental.

Two different modes of preparing the hexa-antipyrine lanthanon iodides have been used. (i) The oxides were dissolved in hydriodic acid to give a neutral solution which, however, contained free iodine. This solution was treated warm with a little antipyrine, producing with the iodine a dark red, highly insoluble precipitate, which became a tar at the b. p. The solution was then free from iodine. Successive quantities of antipyrine (1 mole per mole of iodide) were then added as previously described (*J.*, 1950, 577), and the resulting crystals were cropped. (ii) Owing to the much lower solubility of the complex salt than of lanthanon chlorides, iodides, or antipyrine, it is very satisfactory to prepare a neutral chloride solution and add to it the requisite quantity of potassium or ammonium iodide and antipyrine. Chlorides will then collect at the tail of the fractionation, but trouble from free iodine is not encountered. The thulium series was set up by the first method and the dysprosium series by the second. After fractionation the salt was decomposed by aqueous ammonia; the antipyrine and ammonium iodide solution was filtered from the hydroxides, evaporated, and kept for re-use.

Purification of Lutetium and Thulium.—The series having been set up from 110 g. of oxide rich in lutetium, 40 g. rich in thulium and 80 g. rich in erbium in about 20 flasks, with a total volume of about 17 l., daily fractionation was started. After 12 fractionations much erbium was withdrawn at the tail, and the remaining fractions spread. After 25 fractionations it became possible to start withdrawing pure lutetium at the head. When the hot, nearly saturated solution of the fifth fraction from the head showed no thulium absorption band at 685 mμ. through a 1-l. flask it was considered safe to withdraw the top fraction. Further spreading to about 30 fractions was now required. After 45 fractionations (1000 crystallisations) 90% of the erbium had been eliminated. Only the last three fractions were

rose-coloured. At this stage the mother-liquors of alternate fractions were examined absorptiometrically in 1-cm. layers with a Beckman D.U. spectrophotometer with the following results :

Fraction	3	5	7	9	11	13	15	17	19	21	23	25
Erbium absorption [1]	—	—	—	—	—	0·002	0·004	0·009	0·020	0·040	0·060	0·065
Thulium absorption [2]	0·003	0·005	0·015	0·050	0·061	0·061	0·059	0·054	0·053	0·016	0·007	0·003

[1] Optical density at 525 mμ. (1 g. of Er_2O_3 per l. = 0·0135).
[2] Optical density at 685 mμ. (1 g. of Tm_2O_3 per l. = 0·0123).

The fractions were further spread to number 35 and now fitted into 400-ml. flasks. After 75 fractionations (2000 crystallisations) the bulk of the lutetium had been separated at the head. It was converted into acetate and treated in hot concentrated solution with sodium amalgam (Marsh, *J.*, 1943, 8). This removed several per cent. of ytterbium, and the bulk of the lutetium acetate crystallised on cooling. The remainder was recovered as hydroxide and again converted into acetate. A second sodium amalgam treatment yielded only a small amount of ytterbium; the fourth treatment yielded none. Each treatment consisted of using several successive portions of sodium amalgam, and in the later treatments these were allowed to react only very partially, so that much sodium remained in the mercury when it was separated from the acetate solution. The highly reactive ytterbium, having once passed into the mercury phase, was thereby protected by the even more reactive sodium present in quantity. The recovered lutetium oxide was carefully examined by arc-spectrography (by Johnson, Matthey & Co. Ltd.) but the extremely sensitive ultimate lines of ytterbium were not found. Examined in chloride solution with a hand spectroscope at a concentration equivalent to 670 g. of Lu_2O_3 per l. in 16-cm. depth, the thulium absorption band at 685 mμ. was weak but unmistakable, and comparable with 1 cm. of a solution of 10 g. of pure thulium oxide per l. Thus a thulium content of 0·1% is indicated in the lutetium preparation.

The collected erbium tails were at this stage put through ten series of crystallisations of 10—12 fractions. A little thulium became detectable at the head, but 75 g. of Er_2O_3 were obtained free from thulium. Another 150 g. of salts (oxide content 11%) were set aside containing a little thulium, and 37 g. of salt with considerable thulium content. The thulium fractionation was pursued through another 750 crystallisations. Some ammonium chloride was added to each fraction and is thought to have had a favourable effect on the separation. Heads and tails were collected as seemed desirable. The material was then examined by arc-spectrography. Fractions 37—56 amounted to about 250 g. of salts and ranged from almost pure lutetium (37) to almost pure thulium (56). The yttrium line, 3600·7 A., was faintly visible in fraction 49 and increased in strength down the series. A study of the erbium fractions showed very little variation of the yttrium content, but fraction 86 at the tail of the thulium series showed more yttrium than any of them. A spectrophotometric estimate of fraction 86 gave Tm_2O_3 31%, Er_2O_3 40%, indicating about 30% of yttrium oxide. Comparison was made with a sample of thulium oxide prepared by the late Prof. Sugden (*J.*, 1939, 139) : no trace of yttrium was found in this. Fractions 57—77 were substantially pure thulium and were converted into oxide (25 g.). The green erbium absorption band 525 mμ. was seen in 8·5 cm. of acetate solution (200 g. of Tm_2O_3 per l.) and matched by eye with 5 mm. of a solution of 2·73 g. of Er_2O_3 per l. Thus the erbium content is estimated at 0·3%. The thulium acetate solution was treated with sodium amalgam to withdraw a little ytterbium. An arc-spectrum examination (by Johnson, Matthey & Co. Ltd.) then showed the principal lines of yttrium, two or three faint ultimate lines of ytterbium and lutetium, and two very faint erbium lines.

Less than 3000 crystallisations have served to give large yields of substantially pure lutetium and thulium. It is believed that at some stages the separation suffered from working on too few fractions. A large multiplication of fractions is required in the early stages. In the case of thulium where both head and tail impurities require elimination, a series of 30—40 fractions is required.

The Dysprosium Series.—The oxides used consisted of (approx.) : Y 80 g., Ho 25 g., Dy 180 g., Tb, Gd, etc., 35 g. They gave a series of about 20-l. volume. After 15 series (250 crystallisations) the cold saturated solutions were examined with a Beckman spectrophotometer with the following results :

Fraction	9	12	15	18	21	24
Ho_2O_3, g./l.	0·9	1·3	0·9	0·4	0·5	0·5
Dy_2O_3, g./l.	1·2	3·8	5·1	5·8	6·0	6·9

Thereafter the fractions were increased to number about 32. After 50 series (1500 crystallisations) a similar estimation gave the following results :

Fraction	40	43	46	49	54	59	65	71	76
Ho_2O_3, g./l.	1·75	2·5	2·1	1·0	0·9	0·5	—	—	—
Dy_2O_3, g./l.	2·6	6·1	6·2	5·7	6·4	6·2	6·5	6·2	5·7

The fractions were united in pairs and converted into oxides which were analysed with the following results :

Fraction	38	40	42	44	46	50	54	58	62	66	70	74
Dy_2O_3, %	3	15	51	66	81	88	88	91	93	95	95	74
Ho_2O_3, %	5	17	29	24	22	14	12	7·2	5·2	3·2	2·5	2·5

These fractions totalled 210 g. Yttrium taken off at the head amounted to 80 g., and terbium, etc., at the tail to 30 g.

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THE DYSON PERRINS LABORATORY, OXFORD. [*Received, January 2nd*, 1951.]

297. 1-*Hydroxycyclohexyl* 1-*Hydroperoxide: its Thermal Decomposition and its Reaction with Acyl Chlorides.*

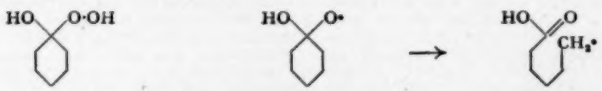
By W. Cooper.

1-Hydroxy*cyclo*hexyl 1-hydroperoxide decomposes when heated, giving free radicals, and the products formed are explicable by the mechanism proposed by George and Walsh (*Trans. Faraday Soc.*, 1946, **42**, 94) for the decomposition of *tert.*-alkyl peroxides. On reaction with acyl chlorides it forms per-esters which are active polymerisation catalysts.

*cyclo*Hexanone reacts with hydrogen peroxide to give 1-hydroxy*cyclo*hexyl 1-hydroperoxide (I), which readily self-condenses to give the peroxides, bis-1-hydroxy*cyclo*hexyl peroxide, 1-hydroperoxy*cyclo*hexyl 1-hydroxy*cyclo*hexyl peroxide, and the dihydroperoxy-peroxide (Milas, Harris, and Panagiotakos, *J. Amer. Chem. Soc.*, 1939, **61**, 2430; Criegee, Schnorrenberg, and Becke, *Annalen*, 1949, **565**, 7).

This paper deals with the reactions of (I), and, though the participation of the peroxides in the decomposition cannot be excluded, their presence does not alter the argument concerning the mechanism of the reaction.

The peroxides are formed in the oxidation of *cyclo*hexanone by Caro's acid or perbenzoic acid, the peroxide link undergoing heterolysis (Friess, *J. Amer. Chem. Soc.*, 1949, **71**, 2571). Thermal decomposition, however, favours homolysis, and, if the mechanism proposed by George and Walsh (*loc. cit.*) holds for these peroxides, the free radicals (II) and (III) would be formed. The usual type of radical-deactivation reactions would then give hexanoic acid, dodecane-1 : 12-dioic acid, and 6-hydroxyhexanoic acid.*



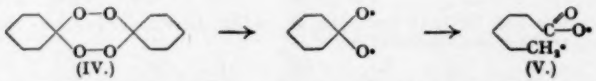
(I.) (II.) (III.)

The products of the thermal decomposition of (I) at 120—160° included the first two of these acids, together with carbon dioxide, water, *cyclo*hexanone, di*cyclo*hexylidene diperoxide (IV), and adipic acid. This last may have resulted from the oxidation of 6-hydroxyhexanoic acid.

Disproportionation of (III) by the reaction

$$2\,(\mathrm{III}) \longrightarrow \mathrm{CH_2{:}CH{\cdot}[CH_2]_3{\cdot}CO_2H} + \mathrm{CH_3{\cdot}[CH_2]_4{\cdot}CO_2H}$$

is unlikely since unsaturated acids were not found, nor was there any appreciable amount of glutaric acid present. There would be little gain in energy to favour such a reaction. Hawkins (*J.*, 1950, 2804) finds that dimerisation of 5-ketohexyl radicals from 1-methyl*cyclo*pentane hydroperoxide is a major reaction.



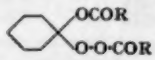
(IV.) (V.)

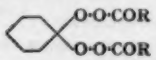
The diperoxide (IV) clearly results from the dehydration of two molecules of the hydroperoxide, since it may be obtained by treating (I) in ether solution with phosphoric oxide or in alcohol with 70% sulphuric acid. It is very stable, and does not liberate iodine from potassium iodide or catalyse vinyl polymerisations. It explodes mildly at 190—200°, giving *cyclo*hexanone and acidic compounds; these were not examined in detail, but, in addition to simple carboxylic acids (probably including hexanoic acid), an insoluble, high-melting polymer was formed. This dissolved in hot alkalis, and was probably derived from the radical (V). In the decomposition of (I), the large amount of *cyclo*hexanone resulted from elimination of hydrogen peroxide, from condensation reactions, or from (II).

The hydroperoxide (I) is a useful polymerisation catalyst, but experiments indicating that

* Geneva nomenclature, $CO_2H = 1$.

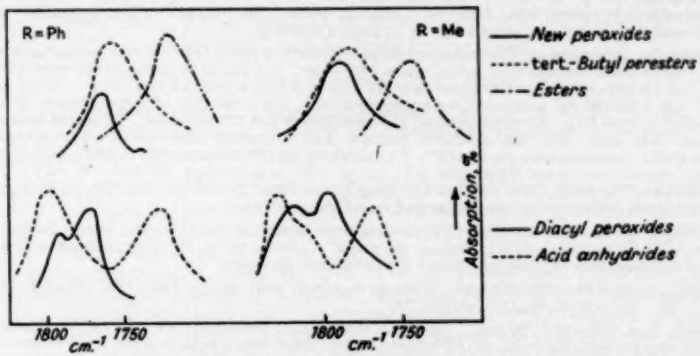
not all of it was consumed in starting polymer chains led to experiments to prepare more efficient acyl derivatives. The hydroperoxide could not be made to react with acyl chlorides in the presence of aqueous alkali, but with an excess of pyridine reaction occurred to form a new series of organic peroxides. Acetyl, benzoyl, *o*-chlorobenzoyl, and *p*-bromobenzoyl derivatives were obtained pure, and also *m*-nitrobenzoyl and phenylacetyl derivatives less pure. The properties of these compounds did not support structure (VI) and, although absolute proof of their structure is lacking, the following evidence suggesting (VII) was obtained : (*a*) Treatment with alcoholic potassium hydroxide gave exclusively the carboxylic acid, *cyclo*hexanone, and

(VI.) 



(VII.)

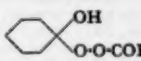
oxygen. (*b*) The benzoyl and *p*-bromobenzoyl derivatives gave 71% and 77% of the corresponding acids. This evidence and the molecular weights show that they contain two acyl and one *cyclo*hexyl group, and also that they are not condensed structures containing more than



Infra-red carbonyl absorption of compounds containing the RCO·O– *grouping.*

one *cyclo*hexyl grouping. (*c*) They are per-esters, and their infra-red spectra show only one carbonyl absorption at the per-ester frequency; (VI) would give one ester and one per-ester frequency, whereas in (VII) negligible mechanical interaction between the two carbonyl groups would give the single absorption (figure). (The infra-red examination formed part of a study on the relation between carbonyl frequency and structure, by Davison, which is now in the press.) The *o*-chlorobenzoyl derivative decomposed faster than the benzoyl derivative, as shown by the rate of polymerisation of styrene, indicating the proximity of the halogen atom to the peroxide link (the relation between peroxide structure and decomposition rate is dealt with in a forthcoming paper). (*d*) The liberation of iodine from acidified potassium iodide, though incomplete, was greater than would be expected for (VI). (*e*) Carbon and hydrogen values were unreliable because of the very explosive character of peroxides, but were in better agreement with structure (VII) than with (VI).

It is difficult to suggest a plausible mechanism for the formation of these peroxides, except by assuming that one molecule of the hydroperoxide is used in the conversion of the acyl chloride into the corresponding peracid, which then reacts with the half acylated compound :



+ RCO·O·OH ⟶ (VII) + H_2O

The evidence for this suggestion is scanty, but two significant facts are that (*a*) three moles of acyl chloride per mole of hydroperoxide were needed to give a reasonable yield of the derivative, and (*b*) the final mixture contained considerable quantities of free carboxylic acid, which showed that water was eliminated at some stage in the reaction. A similar difficulty is presented in the explanation of the mechanism of formation of the dihydroperoxy-peroxide, as this compound cannot be represented by a simple condensation of (I) or its constituents.

The acyl peroxides are efficient catalysts for the polymerisation of styrene. The following table gives results obtained with this monomer at 70°, together with values for the parent hydroperoxide and dibenzoyl peroxide.

Catalyst.	Concentration, g./l.	Concentration, mole/l.*	Polymn. rate, mole/l./sec. $\times 10^4$	$[\eta]$.†
Acetyl derivative	3·25	0·028	1·91	0·52
Benzoyl derivative	4·95	0·028	1·99	0·56
o-Chlorobenzoyl derivative	5·95	0·028	2·35	0·49
Dibenzoyl peroxide	6·80	0·028	1·80	0·47
	3·40	0·014	1·27	0·69
1-Hydroxy*cyclo*hexyl hydroperoxide	1·85	0·014	1·50	0·50

* Calculated on the active-oxygen content of the peroxide. † Intrinsic viscosity of the polymer in benzene.

Experimental.

1-*Hydroxy*cyclo*hexyl* 1-*Hydroperoxide.*—*cyclo*Hexanone was mixed with an equal volume of 30% hydrogen peroxide. Next morning the crystals were removed and recrystallised from alcohol and then light petroleum (b. p. 60—80°). The peroxide had m. p. 79° [Found: equiv. (iodometric), 131; *M* (cryoscopic in benzene), 222. Calc. for $C_6H_{12}O_3$: equiv., 132; *M*, 132]. The molecular weight value was high probably because of association by hydrogen bonding.

Thermal Decomposition of 1-*Hydroxy*cyclo*hexyl* 1-*Hydroperoxide.*—The relative proportions of products isolated varied with temperature in the range 110—160°, but the same compounds were formed in all cases. The hydroperoxide was dropped in small amounts into a flask at 130—140°. A vigorous initial reaction was followed by a smooth decomposition with the evolution of some carbon dioxide. The residue (47·5 g. from 50 g. of hydroperoxide) gave a negative test for peroxide. To it was added N-sodium hydroxide (250 ml.), and the insoluble portion was extracted with ether. The extract (14 g.) was principally *cyclo*hexanone (b. p. 155°; 2 : 4-dinitrophenylhydrazone, m. p. 159°), but in some cases crystalline di*cyclo*hexylidene diperoxide (IV), m. p. 129°, was isolated [Found: C, 63·0; H, 8·75%; *M* (cryoscopic in benzene), 220. Calc. for $C_{12}H_{20}O_4$: C, 63·4; H, 8·8%; *M*, 228]. The aqueous layer gave liquid acids (19 g.) which were separated into three fractions:

(1) 45%, b. p. 95—105°/20 mm. This was mainly hexanoic acid [Found: equiv. (silver salt), 113. Calc. for $C_6H_{12}O_2$: equiv., 116]; anilide, m. p. 95°; amide, m. p. 99° (the melting points were not depressed on admixture of these specimens with authentic samples).

(2) 20%, b. p. 180—220°/20 mm. This gave adipic acid, m. p. 149—150° [Found: equiv. (by titration), 73. Calc. for $C_6H_{10}O_4$: equiv., 73].

(3) 15%, b. p. 220—280°/20 mm. This yellow oil, which deposited crystals on cooling, was extracted several times with large amounts of hot water. When these extracts had cooled there were obtained flat lustrous crystals, which were recrystallised from light petroleum (b. p. 60—80°), ether–light petroleum, and hot water, giving dodecane-1 : 12-dioic acid, m. p. 127°: diamide, m. p. 185°; dianilide, m. p. 169° [Found: C, 62·6; H, 9·9%; equiv. (silver salt and by titration), 113. Calc. for $C_{12}H_{22}O_4$: C, 62·6; H, 9·6%; equiv., 115]. The acid did not depress the m. p. of the synthetic acid prepared from sebacic acid, and showed the same infra-red skeletal absorptions in the 700—1300-cm.$^{-1}$ region. The more water-soluble acids from the decomposition products were isolated and purified through their ethyl esters. Adipic acid was identified, and there was a trace of another acid, very soluble in water, which was probably glutaric acid.

*Decomposition of Di*cyclo*hexylidene Diperoxide.*—This compound (1 g.) was decomposed in small portions at 190—200°. The residue contained neutral products including *cyclo*hexanone, a brown solid which was insoluble in cold dilute alkali or organic solvents, and decomposed before melting, and liquid acids probably containing hexanoic acid. The brown solid dissolved in hot alkalis and on acidification of the alkaline solution regenerated a semi-solid acid, soluble in alcohol.

Reaction of 1-*Hydroxy*cyclo*hexyl Hydroperoxide with Acyl Chlorides.*—The peroxide (1 mole) was dissolved in pyridine (5 moles) and the acyl chloride (3 moles) added slowly, the temperature being kept below 10°. After one hour the mixture was poured into water; acetyl and benzoyl chlorides gave oily products which deposited crystals on cooling, whilst with *m*-nitro- and *p*-bromo-benzoyl chlorides the peroxides were extracted with benzene from the solid precipitate of peroxide and carboxylic acid. The peroxides were recrystallised from benzene–alcohol, precautions being taken because of the explosive nature of the compounds—particularly the acetyl derivative. Boiling the peroxides in alcoholic solution caused decomposition with the formation of the carboxylic acid. The analysis of these compounds was difficult, because of their explosiveness, ease of decomposition in solution, and their incomplete reaction with potassium iodide. The following acyl derivatives were obtained: *benzoyl*, m. p. 97 [Found: C, 67·5; H, 5·9%; *M* (cryoscopic in benzene), 342, 350; (in dioxan), 357; equiv. (iodometric), 186—211. $C_{20}H_{20}O_6$ requires C, 67·5; H, 5·6%; *M*, 356; equiv., 178]; p-*bromobenzoyl*, m. p. 104° [Found: Br, 31·6%; *M* (in benzene), 471; equiv. (iodometric), 260—300. $C_{20}H_{18}O_6Br_2$ requires Br, 31·2%; *M*, 514; equiv., 257]; o-*chlorobenzoyl*, m. p. 70° [Found: *M* (benzene), 378; equiv., 205. $C_{20}H_{18}O_6Cl_2$ requires *M*, 425; equiv., 212·5]; *m*-nitrobenzoyl, m. p. 116°, not obtained pure; *acetyl*, m. p. 73° [Found: *M* (benzene), 210, 230; equiv., 129—131. $C_{10}H_{16}O_6$ requires *M*, 232; equiv., 116].

Formation of a Carboxylic Acid during the Preparation of Acyl Derivatives.—The hydroperoxide (1·5 g.) in pyridine was treated with *p*-bromobenzoyl chloride (6 g.), and the mixture poured into light petroleum and filtered. The solid was washed with benzene, and the pyridine hydrochloride removed; there was left *p*-bromobenzoic acid (m. p. 220°) (1·9 g.). The petroleum–benzene extracts were shaken

with dilute ammonia solution, giving more (0·3 g.) of the carboxylic acid. The upper layer after removal of solvents gave crude peroxide (3·3 g.).

Reaction with Alcoholic Alkalis.—The peroxides dissolved readily in benzene and the addition of alcoholic potassium hydroxide to the solution caused an immediate liberation of oxygen. The residue after the solvents had been removed by distillation was acidified and the carboxylic acid extracted quantitatively. The distillate contained *cyclo*hexanone (2 : 4-dinitrophenylhydrazone, m. p. 159—160°).

The experimental details of the polymerisation of styrene, and the examination of the polymers are given in a paper to be published later.

The author thanks Mr. W. H. T. Davison for the infra-red examination of the peroxides, and the Dunlop Rubber Company for permission to publish this work.*

CHEMICAL RESEARCH DIVISION,
FORT DUNLOP, BIRMINGHAM. [*Received, January 16th*, 1951.]

* This work formed a part of a Ph.D. thesis, University of London, 1950.

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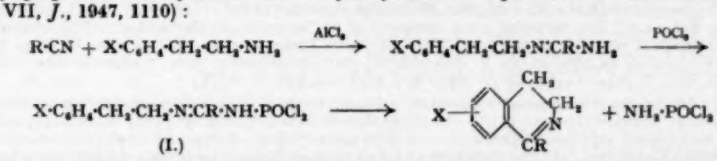
298. *Amidines. Part XVI. A New Synthesis of* 1-*Alkyl- and* 1-*Aryl*-3 : 4-*dihydroisoquinolines.*

By C. I. BRODRICK and W. F. SHORT.

1-Alkyl- and 1-aryl-3 : 4-dihydro*iso*quinolines are produced by heating *N*-2-arylethyl derivatives of aliphatic and aromatic amidines and phosphoryl chloride in nitrobenzene solution.

THE most important methods for the synthesis of *iso*quinolines start from 2-arylethylamines, which yield 3 : 4-dihydro*iso*quinolines on successive acylation and dehydration, and tetrahydro-*iso*quinolines by ring closure of their alkylidene and arylidene derivatives. The first method, discovered by Bischler and Napieralski (*Ber.*, 1893, **26**, 1903) and generalised and improved by Pictet and his co-workers (*ibid.*, 1909, **42**, 1973, 1979), by Decker and Kropp (*ibid.*, p. 2075), by Decker, Kropp, Hoyer, and Becker (*Annalen*, 1913, **395**, 299), and by Whaley and Hartung (*J. Org. Chem.*, 1949, **14**, 650), has found considerable application in the synthesis of *iso*quinoline alkaloids. We find that a similar synthesis can be achieved by removing the elements of ammonia from the *N*-2-arylethyl derivatives of aliphatic and aromatic amidines, which are readily prepared from cyanides and 2-arylethylamines in presence of aluminium chloride (Part VII, *J.*, 1947, 1110) :



An acid reagent and a high temperature are necessary for the reaction, and the best results are obtained with phosphoryl chloride (*ca.* 10 mols.) in boiling nitrobenzene. Derivatives of amino-phosphonyl dichloride (I) are described in a subsequent communication. The following 3 : 4-dihydro*iso*quinolines were prepared from the corresponding amidines; the yields recorded in parentheses are not necessarily the highest obtainable since a thorough examination of the experimental conditions was not made: 1-phenyl- (48%); 1-benzyl- (22%); 1-*p*-methyl-sulphonylphenyl- (80%); 1-*p*-methoxyphenyl- (31%); 6 : 7-dimethoxy-1-phenyl- (42%); 1-3′-pyridyl- (51%); and 1-amyl- (43·5%). The dihydro*iso*quinolines should not be distilled at atmospheric pressure since we have shown that they undergo disproportionation under these conditions (*J.*, 1949, 2587); they can be dehydrogenated or oxidised to *iso*quinolines by standard methods.

EXPERIMENTAL.*

Preparation of Amidines.—In the formation of the amidines the general procedure was that described for *N*-2-phenylethylbenzamidine, except that, in other cases, the melt was allowed to cool without further heating, the temperature in parentheses after the quantity of the reactants being the maximum attained. Usually a large volume of water was necessary to decompose the reaction mixture and dissolve the sparingly soluble amidine hydrochloride, which may be salted out as an oil.

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* See also B.P. 642,286/1948.

N-2-*Phenylethylbenzamidine*. Powdered anhydrous aluminium chloride (13·4 g., 1·0 mol.) was added during 20—30 seconds to a stirred mixture of phenyl cyanide (10·3 g., 1·0 mol.) and 2-phenylethylamine (12·1 g., 1·0 mol.). The temperature rose rapidly to 220° and then fell; the melt was finally heated to 165—175° for 30 minutes, then cooled to 130°, and poured into water (500 c.c.). The warm solution was filtered (Supercel) and the unchanged cyanide (0·2 g., 1·95%) extracted with ether. Aqueous sodium hydroxide was added to *ca.* pH 11 and the crude base isolated as a brown oil (18·9 g.) by extraction with benzene. The oil was dissolved in dry ether (300 c.c.) and treated with dry hydrogen chloride, and the sticky precipitate crystallised from methanol–ether to give thin, colourless prisms, m. p. 182—183°, of N-2-*phenylethylbenzamidinium chloride* (14·3 g., 55%) (Found : C, 68·65; H, 6·5; N, 11·0. $C_{18}H_{17}N_2Cl$ requires C, 69·1; H, 6·5; N, 10·75%). The *picrate* crystallised from ethanol in lemon-yellow prisms, m. p. 173—174° (Found : N, 15·6. $C_{21}H_{19}O_7N_5$ requires N, 15·45%), but the free amidine was only obtained as an oil.

The mother-liquors from the crystallisation of the hydrochloride were evaporated and the residue was treated with an aqueous solution of sodium picrate to give mixed picrates (5·9 g.), m. p. 100—120°, a portion (1·5 g.; m. p. 167—170°) remaining undissolved on extraction with warm ethanol (50 c.c.). Crystallisation from a large volume of ethanol gave yellow prisms, m. p. 170—171°, of NN'-*bis*-2-*phenylethylbenzamidinium picrate* (Found : C, 62·0; H, 4·9; N, 12·7. $C_{32}H_{27}O_7N_8$ requires C, 62·5; H, 4·85; N, 12·6%). Fractional crystallisation of the product obtained from the ethanol liquors yielded the picrate of the *N*-monosubstituted amidine.

In an experiment in which poor-quality aluminium chloride was inadvertently used the only product isolated was the *NN'*-disubstituted picrate (3·5%), together with unchanged cyanide (74%) and amine (60%).

The amidine hydrochloride was also prepared by the Pinner route in 47% yield; the low yield may be due to the incidental access of moisture, since benzo-2-phenylethylamide was isolated as a by-product.

α-*Phenyl*-N-2-*phenylethylacetamidine*. Benzyl cyanide (23·4 g.), 2-phenylethylamine (24·2 g.), and aluminium chloride (26·8 g.) (240°) afforded α-*phenyl*-N-2-*phenylethylacetamidinium chloride* (15·5 g., 28%) as colourless prisms, m. p. 173·5—174·5° (Found : N, 10·1. $C_{16}H_{19}N_2Cl$ requires N, 10·2%). The *picrate* crystallised from ethanol in needles, m. p. 113—114° (Found : N, 15·35, 15·4. $C_{22}H_{21}O_7N_5$ requires N, 15·0%).

In another experiment the melt was further heated at 185° for 45 minutes; the yield of hydrochloride was then 21%, and benzyl cyanide (13%), contaminated with a small amount of an unidentified substance, m. p. 82—84°, was recovered unchanged.

p-*Methylsulphonyl*-N-2-*phenylethylbenzamidine*. Powdered *p*-cyanophenyl methyl sulphone (18·1 g.), 2-phenylethylamine (12·1 g.), and aluminium chloride (13·4 g.) (190°) afforded unchanged cyanide (0·47 g., 2·6%) and crude amidine as a brown, viscous gum (28 g.). It was converted into the *hydrochloride* by trituration with 2N-hydrochloric acid (110 c.c.) and recrystallising the insoluble material from methanol–ether as colourless plates, m. p. 264—265° (uncorr.) (18·5 g., 55%) (Found : N, 8·4. $C_{16}H_{19}O_2N_2ClS$ requires N, 8·3%). The *picrate* crystallised from ethanol in elongated plates, m. p. 168—168·5° (Found : N, 13·2. $C_{22}H_{21}O_9N_5S$ requires N, 13·2%).

p-*Methoxy*-N-2-*phenylethylbenzamidine*. The reaction mixture from *p*-methoxyphenyl cyanide (13·3 g.), 2-phenylethylamine (12·1 g.), and aluminium chloride (13·4 g.) (140°) was cooled and triturated with water (25 c.c.). The insoluble solid consisted of unchanged cyanide (2·94 g., 22%), removed by repeated extraction with ether, and p-*methoxy*-N-2-*phenylethylbenzamidinium chloride* (15·26 g., 52·5%) which was obtained as needles, m. p. 223—223·5°, on crystallisation from methanol–ether (Found : C, 66·1; H, 6·4; N, 9·7. $C_{16}H_{19}ON_2Cl$ requires C, 66·1; H, 6·5; N, 9·6%).

N-2-(3 : 4-*Dimethoxyphenyl*)*ethylbenzamidine*. Phenyl cyanide (8·8 g.), homoveratrylamine (14·32 g.), and aluminium chloride (10·4 g.) (210°) (frothing then occurred, probably owing to demethylation, so the melt was cooled rapidly) afforded recovered cyanide (3·6 g., 41%) and crude amidine (7·55 g.) (isolated with chloroform). It was dissolved as far as possible in aqueous lactic acid and extracted with benzene to remove insoluble material, and the dry, benzene solution of the regenerated base treated with dry hydrogen chloride. The *hydrochloride* was recrystallised several times from methanol–ether as colourless plates, m. p. 200·5—201·5° (3·5 g., 13%) (Found : C, 63·5; H, 6·8; N, 8·9. $C_{17}H_{21}O_2N_2Cl$ requires C, 63·65; H, 6·55; N, 8·7%). The *picrate* crystallised from ethanol in orange-yellow needles, m. p. 165—166° (Found : N, 13·8. $C_{23}H_{23}O_9N_5$ requires N, 13·65%).

N-2-*Phenylethylnicotinamidine*. 3-Cyanopyridine (10·4 g.), 2-phenylethylamine (12·1 g.), and aluminium chloride (13·4 g.) (210°) gave the crude amidine as a gum (14·0 g.), which crystallised on treatment with ether. The brown solid (8·1 g., 36%; m. p. *ca.* 118—129°) afforded dense prisms of N-2-*phenylethylnicotinamidine*, m. p. 131—131·5°, on crystallisation first from benzene and then from ethyl acetate (Found : C, 74·8; H, 6·5; N, 18·8. $C_{14}H_{15}N_3$ requires C, 74·7; H, 6·7; N, 18·7%). With alcoholic picric acid it formed the *dipicrate*, rosettes of prisms (from ethanol), m. p. 174—175° (Found : C, 45·7; H, 3·1. $C_{26}H_{21}O_{14}N_9$ requires C, 45·7; H, 3·1%).

N-2-*Phenylethylhexanamidine* (with D. A. Firth). The reaction mixture from amyl cyanide (8 g.), 2-phenylethylamine (10 g.), and aluminium chloride (11 g.) (170°) was treated with ice-water (50 c.c.) and extracted with benzene. The insoluble oil which formed at the interface was dissolved in water (600 c.c.) and treated with aqueous benzenesulphonic acid [20 c.c. of 70% (w/v)]. The amidine *benzenesulphonate* which separated crystallised from water in white plates, m. p. 74—75° (6·9 g., 22%) (Found : N, 7·6. $C_{20}H_{18}O_3N_2S$ requires N, 7·45%).

Preparation of Dihydroisoquinolines.—3 : 4-*Dihydro*-1-*phenylisoquinoline*. *N*-2-Phenylethylbenzamidinium chloride (7·8 g.) was refluxed with nitrobenzene (81 c.c.) and phosphoryl chloride (27 c.c.) for 2·5 hours. Hydrogen chloride was evolved and the internal temperature rose from about 150° to 170°.

The excess of phosphoryl chloride and nitrobenzene were removed by distillation at 1 mm. (bath, 100°), and the residue was heated with excess of aqueous sodium hydroxide. The insoluble oil was extracted with benzene and distilled to give 3 : 4-dihydro-1-phenyl*iso*quinoline, b. p. 145—155°/1—2 mm. (2·68 g., 43%) (the forerun containing nitrobenzene gave a further 4·8% as picrate). After dilution with light petroleum (2 volumes) it was filtered from a small amount of solid and then distilled at 139—142°/0·75 mm. (Found : C, 86·4; H, 6·2; N, 6·65. Calc. for $C_{15}H_{13}N$: C, 86·95; H, 6·3; N, 6·8%). The identity of the product was confirmed by comparison of the properties of the base (absorption spectrum and disproportionation on heating at atmospheric pressure), the picrate, m. p. 173—174° (Found : C, 57·8; H, 3·4; N, 12·9. Calc. for $C_{21}H_{16}O_7N_4$: C, 57·8; H, 3·7; N, 12·8%), and the hydrochloride, m. p. 236—238° (Found : C, 73·4; H, 6·0; N, 5·6. Calc. for $C_{15}H_{14}NCl$: C, 73·9; H, 5·75; N, 5·75%), with authentic specimens, prepared as described by Brodrick and Short (*loc. cit.*) (Whaley and Hartung, *loc. cit.*, record m. p. 178° for the picrate and 245—248° for the hydrochloride).

3 : 4-*Dihydro*-1-p-*methylsulphonylphenylisoquinoline*. (i) When *p*-methylsulphonyl-*N*-2-phenylethylbenzamidinium chloride (6·8 g.) was treated similarly for 4 hours the product solidified on evaporation of the benzene extract. Crystallisation from methanol gave brownish prisms, m. p. 152—154° (4·02 g., 70%), and further crystallisation from ethyl acetate–light petroleum afforded the pure dihydro*iso*quinoline as almost colourless prismatic needles, m. p. 156·5° (Found : C, 67·5; H, 5·35; N, 5·0. $C_{16}H_{15}O_2NS$ requires C, 67·4; H, 5·3; N, 4·9%). The methanolic mother-liquor, with picric acid, gave the *picrate* (1·0 g., 9·7%; m. p. 186—189°), which crystallised from methanol–acetone in yellow plates and needles, m. p. 192—192·5° (Found : N, 10·85. $C_{22}H_{18}O_9N_4S$ requires N, 10·9%). The *hydrochloride* formed almost colourless prisms (from methanol–ether), m. p. 267—268°, sintering slightly at 262° (Found : N, 4·4. $C_{16}H_{16}O_2NClS$ requires N, 4·35%).

(ii) The amidine hydrochloride (2·3 g.), nitrobenzene (21 c.c.), and phosphoric oxide (4·6 g.) were refluxed for 1 hour. The solid was separated by decantation and cautiously decomposed with water. The dihydro*iso*quinoline, m. p. 156—157° (yield, 15%), and picrate, m. p. 193—194°, were identical with the products obtained in (i).

(iii) By use of xylene and phosphoryl chloride the dihydro*iso*quinoline was obtained in 31% yield.

3 : 4-*Dihydro*-1-p-*methoxyphenylisoquinoline*. Reaction of *p*-methoxy-*N*-2-phenylethylbenzamidinium chloride (2·9 g.) under the usual conditions for 5 hours gave an oil which was converted into the *hydrochloride*, crystallising from methanol–ether in colourless prisms (0·95 g., 31%), containing solvent of crystallisation, m. p., if entered at *ca.* 80° and heated slowly, 199—200° (Found, on air-dried substance : C, 67·2; H, 5·8; N, 4·7. $C_{16}H_{15}ONCl,CH_3{\cdot}OH$ requires C, 66·8; H, 6·55; N, 4·6%). When the material was dried at 100° it melted at 212—214° (entering at 204°) (Found : C, 70·5; H, 5·4; N, 5·2. $C_{16}H_{14}ONCl$ requires C, 70·2; H, 5·85; N, 5·1%), but when kept it was readily converted into the *dihydrate* (Found : loss at 100°/1 mm., 11·7; on dried material, C, 70·3; H, 6·1. $C_{16}H_{14}ONCl,2H_2O$ requires H_2O, 11·6%). The *picrate* formed fine, hair-like needles (from methanol), m. p. 161·5° (Found : N, 12·3, 12·35. $C_{22}H_{16}O_8N_4$ requires N, 12·0%).

3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-*phenylisoquinoline*. Prepared similarly from the amidine hydrochloride (2·7 g.) by reaction for 2 hours, this dihydro*iso*quinoline crystallised from benzene–light petroleum in almost colourless, prismatic needles, m. p. 119·5—120·5° (0·95 g., 42%) (Found : N, 5·5. Calc. for $C_{17}H_{17}O_2N$: N, 5·25%) (Harwood and Johnson, *J. Amer. Chem. Soc.*, 1934, **56**, 468, record m. p. 120·5—121·5°, and Sugasawa, *J. Pharm. Soc. Japan*, 1935, **55**, 224, m. p. 120—121°).

3 : 4-*Dihydro*-1-3′-*pyridylisoquinoline*. The amidine (2·84 g.) was allowed to react for 3 hours and worked up as usual. Distillation of the benzene extract gave the *dihydroisoquinoline* as a colourless oil, b. p. 155—159°/0·8 mm. (1·33 g., 51%), which was redistilled (b. p. 155°/0·5 mm.) for analysis (Found : C, 80·7; H, 5·5; N, 13·5. $C_{14}H_{12}N_2$ requires C, 80·8; H, 5·8; N, 13·5%). The *dipicrate* crystallised from ethanol–acetone in clusters of fine, prismatic needles, m. p. 196—197° (Found : C, 46·7; H, 2·7; N, 16·9. $C_{26}H_{16}O_{14}N_8$ requires C, 46·85; H, 2·7; N, 16·8%).

1-*Amyl*-3 : 4-*dihydroisoquinoline* (with D. A. Firth). *N*-2-Phenylethylhexanamidine (0·75 g.), prepared as an oil from the benzenesulphonate, was allowed to react by the general method for 2·5 hours. The crude 1-amyl-3 : 4-dihydro*iso*quinoline was obtained as a gum (0·3 g., 43·5%) which was converted into the *picrate*, needles (from ethanol), m. p. 112·5—113° (Found : N, 13·4. $C_{20}H_{22}O_7N_4$ requires N, 13·0%).

Thanks are expressed to Mr. R. J. Kemp for experimental assistance and to Mrs. M. Ward and Mrs. F. Weston for the semi-micro-analyses.

Research Laboratories, Messrs. Boots Pure Drug Co. Ltd.,
Nottingham. [*Received, January 30th*, 1951.]

299. *The Seed Oil of* Onguekoa Gore *Engler. Part I. The Position of the Hydroxyl Group in the Unsaturated Monohydroxy-C_{18} Acid (or Acids).*

By J. P. Riley.

The unsaturated hydroxy-acid (or possibly, -acids) of the seed fat of *Onguekoa Gore* Engler has been shown to yield on hydrogenation 8-hydroxystearic acid,* and thus the original unsaturated acid must be a straight chain C_{18} acid bearing a hydroxyl group on its eighth carbon atom.

The tree *Onguekoa Gore* Engler syn. *Ongokea klaineana* Pierre (also known by the native names Boleka and Isano) grows wild in Equatorial Africa. It bears soft pulpy yellow fruits about 1" in diameter, which contain buff-coloured kernels. The latter yield on extraction 60—80% of a somewhat viscous reddish oil having a rather unpleasant smell.

Steger and van Loon (*Fette u. Seifen*, 1937, **44**, 243) isolated from the oil a highly unsaturated acid to which they assigned the formula :

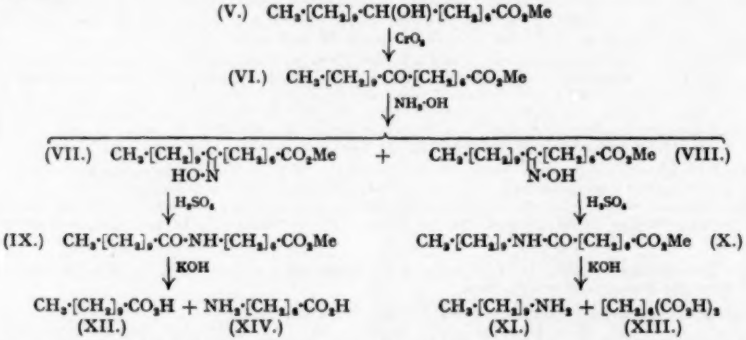
either $CH_3\cdot[CH_2]_7\cdot CH{=}CH\cdot CH_2\cdot C{\equiv}C\cdot[CH_2]_4\cdot CO_2H$ (I.) or $CH_3\cdot[CH_2]_7\cdot C{\equiv}C\cdot CH_2\cdot CH{=}CH\cdot[CH_2]_4\cdot CO_2H$ (II.)

The same workers also prepared from the oil an acid, m. p. 38—39°, which they called isanic acid. Castille (*Annalen*, 1939, **543**, 104), who also isolated this compound and named it erythrogenic acid, was able to show that its formula was

either $CH_2{=}CH{-}C{\equiv}C\cdot[CH_2]_4\cdot C{\equiv}C\cdot[CH_2]_7\cdot CO_2H$ (III.) or $CH_2{=}CH\cdot[CH_2]_4\cdot C{\equiv}C\cdot C{\equiv}C\cdot[CH_2]_7\cdot CO_2H$ (IV.)

These deductions were confirmed by Steger and van Loon (*Rec. Trav. chim.*, 1940, **59**, 1156) who proved that isanic acid is (IV).

From the hydrogenated mixed esters of the oil, Steger and van Loon (*loc. cit.*) obtained a hydroxy-acid, m. p. 75—78°, which they considered to be a monohydroxystearic acid not identical with 12-hydroxystearic acid, and which they later showed to be either 8- or 9-hydroxystearic acid.*



It was with the aim of determining the position of the hydroxyl group unequivocally that the present work was carried out. A concentrate of the unsaturated hydroxy-acid was prepared by low-temperature crystallisation of the mixed acids from the oil, which were esterified with methyl alcohol and hydrogenated at 105° using Raney nickel. The hydrogenated ester was acetylated and fractionally distilled to remove saturated esters and polymerised material. The recovered acetylated esters were hydrolysed, re-esterified with methyl alcohol, and then submitted to the process first used by Baruch (*Ber.*, 1894, **27**, 127) in the elucidation of the structure of oleic acid, and more recently employed by Ross, Gebhart, and Gerecht (*J. Amer. Chem. Soc.*, 1949, **71**, 283) for the examination of peroxidised methyl oleate. The methyl hydroxystearate (V) was oxidised

* Geneva numbering (CO_2H = 1).

with chromium trioxide to the corresponding methyl ketostearate (VI), and the latter converted into its oximes (VII and VIII). The oximes were submitted to the Beckmann rearrangement and the resulting mixture of amides (IX and X) was hydrolysed, yielding *n*-decylamine (XI), undecanoic acid (XII), and suberic acid (XIII) [the amino-acid (XIV) was not isolated]. These products indicate that the hydroxy-acid formed by hydrogenation of the unsaturated hydroxy-acid present in the oil is 8-hydroxyoctadecanoic acid.

Experimental.

Seeds of *Onguekoa Gore* Engler from the Cameroons were extracted first with light petroleum (b. p. 40—60°) and then with ether, giving an oil with the following characteristics :

	Petroleum-extracted oil.	Ether-extracted oil.
Yield	15·4%	45·2%
Colour	Light yellow	Dark brown
Free fatty acid (as oleic)	49·3%	36·3%
Iodine value (Wijs, 30 minutes)	205·8	198·4
Acetyl value *	—	89·3
Saturated acids (Bertram)	2·5%	1·8%
Unsaponifiable	3·2%	5·3%

* Of methyl esters of the mixed acids.

Preparation of a Concentrate of the Unsaturated Hydroxy-acid.—The ether-extracted oil (130 g.) was hydrolysed for 1 hour with boiling 10% alcoholic potassium hydroxide (650 ml.), and the unsaponifiable matter [8·28 g.; I.V. (Wijs) 290·9] was extracted with ether. The recovered acids (116·9 g.) were boiled four times with 300-ml. portions of light petroleum (b. p. 40—60°) and kept overnight at 0° before the upper layer was decanted. The petrol-insoluble acids [42·2 g.; I.V. (Toms) 177·9; $E^{1\%}_{1\,cm.}$ at 239 mμ., 96·1; at 253 mμ., 88·1; at 267 mμ., 90·8; at 283 mμ., 81·4] were esterified at room temperature with 200 ml. of methyl alcohol containing 0·5% of hydrogen chloride, yielding 40·4 g. of neutralised methyl esters [I.V. (Toms) 198·9].

Hydrogenation.—The methyl esters (20·45 g.) were hydrogenated at 105° using Raney nickel catalyst (Pavlic and Adkins, *J. Amer. Chem. Soc.*, 1946, **68**, 1471), 3·54 l. of hydrogen (at N.T.P.) being absorbed. The hydrogenated ester had I.V. (Wijs) 30·6, hence the iodine value of the original ester was 228.

Acetylation.—The hydrogenated ester (20·2 g.) was acetylated under reflux with 20 ml. of acetic anhydride for 2 hours. The excess of anhydride was destroyed by boiling with water for 1 hour. The acetylated product was extracted with ether, and acetic acid removed by washing with 10% aqueous potassium hydroxide. The acetyl compound (20·65 g.) was fractionally distilled under reduced pressure through a packed and electrically heated column to remove non-hydroxy-esters and polymerised material.

Fraction.	G.	B. p./*ca.* 0·1 mm.	Sap. equiv.	I.V.	Fraction.	G.	B. p./*ca.* 0·1 mm.	Sap. equiv.	I.V.
1	1·81	up to 132°	215·3	9·8	5	3·25	173°	173·1	—
2	2·11	132—148	288·4	7·8	6	1·41	173 falling	175·4	25·0
3	2·54	148—158	269·4	5·5	7	0·82	Column washings	183·2	—
4	2·58	160—172	206·8	—	8	5·40	Residue	224·9	65·9
					Total	19·92			

The fatty acids obtained by hydrolysis of fractions 4—7 (total, 6·71 g.) were combined and esterified with 30 ml. of methyl alcohol containing 0·5% of hydrogen chloride; the yield of methyl ester was 5·86 g.

Oxidation of Methyl Esters (V).—The methyl ester (5·86 g.) in acetic acid (60 ml.) was oxidised at room temperature with a 10% solution of chromium trioxide in acetic acid (24 ml.). The reaction was somewhat exothermic and the flask was cooled in running water. After 30 minutes at room temperature, the reaction mixture was poured into water (500 ml.), and sulphur dioxide was passed into the solution. The resultant keto-ester was extracted with ether, and the ethereal extract washed several times with water and then with 10% aqueous potassium hydroxide. The ether was removed by distillation after being washed free from alkali, yielding methyl 8-ketostearate (VI) (5·24 g.), m. p. 42·7—44·3°.

Preparation of the Oximes (VII *and* VIII) *from Methyl Ketostearate.*—Methyl 8-ketostearate (5·22 g.) in 80% alcohol (45 ml.) was treated with solutions of hydroxylamine hydrochloride (4 g.) in 80% alcohol (15 ml.) and of fused sodium acetate (6 g.) in 80% alcohol (15 ml.). The mixture was boiled under reflux for 2 hours and most of the alcohol was then distilled off. The product was poured into water, and the mixed oximes (VII and VIII) were extracted with ether. The mixed oximes (5·40 g.) consisted of a light yellow oil which did not solidify at −10°.

Beckmann Rearrangement.—The mixture of oximes (5·40 g.) was heated with concentrated sulphuric acid (30 ml.) at 100° for 1 hour. The product, when cool, was poured on ice (100 g.), and the mixed amides (IX and X) (5·21 g.) were separated by filtration, washed with water till free from acid, and dried *in vacuo*.

Hydrolysis of the Amides (IX *and* X).—The mixed amides (5·11 g.) were heated in a steel bomb at 170° for 3 hours with 30% potassium hydroxide solution (20 ml.). After cooling, the bomb was opened and the aqueous liquid was acidified with sulphuric acid and steam-distilled, 2 l. of distillate being collected and retained for extraction of the steam-volatile acid (XII). The residue from the steam-distillation

was extracted with ether, when 1·31 g. of a mixture of dibasic acid (XIII), unhydrolysed amide, and saturated acid (?) were obtained. The aqueous residue from the extraction was made alkaline with sodium hydroxide solution and steam-distilled; 1·5 l. of distillate were collected and gave, on extraction with ether, 1·58 g. of volatile amine (XI) which was purified by distillation under reduced pressure (b. p. 108°/12 mm.). The amino-acid (XIV) in the aqueous residue from the steam-distillation was not recovered.

(a) *Steam-volatile acid* (XII). The distillate (2 l.) obtained from the acidic solution was extracted with ether, and 0·852 g. of undecanoic acid was recovered (Found: S.E., 187·0. Calc. for $C_{11}H_{21}\cdot CO_2Me$: S.E., 186·0); the *p*-bromophenacyl ester had m. p. 67—68° alone or mixed with authentic *p*-bromophenacyl undecanoate (m. p. 67—68°).

(b) *Dibasic acid* (XIII). The brownish solid (1·31 g.) extracted with ether from the acidic steam-distillation residue was boiled with three 200-ml. portions of water, and the aqueous extracts were filtered hot through a fine filter paper to remove an insoluble dark oil (0·708 g.) which was rejected. The combined aqueous solutions were evaporated to 20 ml. and cooled to room temperature, the precipitated dibasic acid (0·377 g.; m. p. 126—131°) was filtered off and recrystallised twice from 20 ml. of water at 0° and twice from 15 ml. of ethyl acetate at 0°, yielding 0·105 g. of dibasic acid [Found: S.E., 87·3. Calc. for $C_8H_{14}(CO_2H)_2$: S.E., 87·0], m. p. 138·5—140·3° alone or mixed with suberic acid (m. p. 139—141°).

(c) *Steam-volatile amine* (XI). The distilled amine (0·256 g.) in ligroin (b. p. 80—100°) (10 ml.) was treated with a solution of α-naphthyl *iso*cyanate (0·30 g.) in ligroin (b. p. 80—100°) (10 ml.). The resultant gelatinous solid was filtered off, pressed, washed with light petroleum (b. p. 40—60°), and dried *in vacuo*. The crude product (0·127 g.) was recrystallised from ligroin and yielded *N*-*n*-decyl-*N*′-α-naphthylurea, m. p. 128—129° alone or mixed m. p. with an authentic specimen (m. p. 128—129°).

The author thanks Professor T. P. Hilditch for his guidance and valued criticism during the course of this work.

THE UNIVERSITY, LIVERPOOL. [*Received, February 8th*, 1951.]

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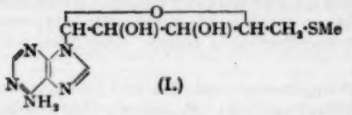
300. *Adenine 5′-Deoxy-5′-methylthiopentoside (Adenine Thiomethyl Pentoside): A Proof of Structure and Synthesis.*

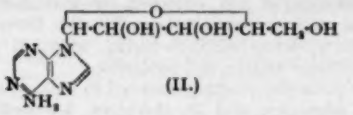
By J. BADDILEY.

5′-Deoxy-5′-methylthioinosine (V) has been synthesised from 2′ : 3′-*iso*propylidene 5′-toluene-*p*-sulphonyl inosine (III) by replacement of the toluene-*p*-sulphonyl by a methylthio-group, followed by hydrolysis of the *iso*propylidene residue. Its identity with hypoxanthine deoxymethylthiopentoside, obtained by deamination of natural "adenine thiomethyl pentoside," was shown. This establishes the structure of the latter as 9-(5′-deoxy-5′-methylthio-β-D-ribofuranosyl)adenine, a synthesis of which is also reported.

THE nucleoside often known as "adenine thiomethyl pentoside" or "adenyl thiomethyl pentose" was first isolated from yeast by Mandel and Dunham (*J. Biol. Chem.*, 1912, **11**, 85) and later by Suzuki (*J. Tokio Chem. Soc.*, 1914, **34**, 1134), Levene (*J. Biol. Chem.*, 1924, **59**, 465), Euler and Myrbäck (*Z. physiol. Chem.*, 1928, **177**, 237), and others. The early workers failed to detect the presence of sulphur in their materials, and the substance was formulated as an adenine hexoside. Not until 1924 did Suziki, Ohdake, and Mori (*Biochem. Z.*, 1924, **154**, 278) establish the correct formula, $C_{11}H_{15}O_3N_5S$. The sulphur atom was located in the carbohydrate moiety since acid hydrolysis of the nucleoside gave adenine and a sugar containing sulphur. Levene and Sobotka (*J. Biol. Chem.*, 1925, **65**, 551) and Sobotka (*J. Biol. Chem.*, 1926, **69**, 267) considered that this sugar was probably a ketose containing one methylthio- or methoxy-group, but it was recognised later as an aldose by Wendt (*Z. physiol. Chem.*, 1942, **272**, 152). Periodate titration of both the free sugar and the thiopentitol obtained from it on reduction and application of the Böeseken test for *cis*-hydroxyl groups strongly suggested that the sugar was 5-deoxy-5-methylthioribose (Satoh and Makino, *Nature*, 1950, **165**, 769). Evidence in support of this formulation has been obtained by Weygand, Trauth, and Löwenfeld (*Chem. Ber.*, 1950, **83**, 563), who showed that the osazone of the natural sugar was identical with that of synthetic 5-deoxy-5-methylthio-D-arabinose. As the free sugars themselves were not identical this was evidence that the natural one was 5-deoxy-5-methylthio-D-ribose. The position of attachment of the thio-sugar in the nucleoside was assigned to $N_{(9)}$ (as in I) by Falconer and Gulland on the basis of spectroscopic evidence (*J.*, 1937, 1912). The configuration about the glycosidic centre had not been established.

A synthesis of this substance seemed highly desirable, not only to confirm the structure (I) and determine the configuration about the glycosidic linkage, but also to make this interesting but inaccessible nucleoside more readily available for biological study. Its known pharmacological effects (Kuhn and Henkel, *Z. physiol. Chem.*, 1941, **269**, 41; Ewing and Schlenk, *J. Pharmacol.*


(I.)

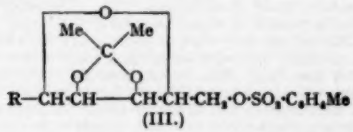

(II.)

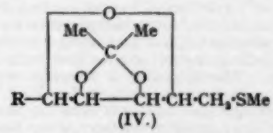
Exper. Therap., 1943, **79**, 164) and probable biological activity (Nakahara, Inugai, Ugami, and Nagata, *Sci. Jap. Inst. Phys. Chem. Res.*, 1945, **42**, 153) are worthy of further study as is the suggestion that it may participate in biological methylation processes (Lipmann, *Adv. Enzymol.*, 1941, **1**, 99).

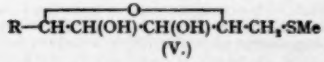
If it is assumed that "adenine thiomethyl pentoside," like other naturally occurring nucleosides, is a β-glycoside, then it should be possible to synthesise it from adenosine (II) by substitution of the primary hydroxyl at position 5′ by a methylthio-group inasmuch as the structure of adenosine is fully established as 9-β-D-ribofuranosyladenine (*inter al.*, Davoll, Lythgoe, and Todd, *J.*, 1946, 833; 1948, 967; Lythgoe, Smith, and Todd, *J.*, 1947, 355). The envisaged synthesis involved the introduction of a toluene-*p*-sulphonyl group in the 5′-position in 2′ : 3′-*iso*propylidene adenosine, followed by its replacement by methylthio- and hydrolysis of the *iso*propylidene residue. Considerable difficulty was experienced, however, in the preparation of the necessary toluene-*p*-sulphonate in a pure state. Reaction between toluene-*p*-sulphonyl chloride and 2′ : 3′-*iso*propylidene adenosine under various conditions gave syrupy products from which some unchanged *iso*propylidene compound was usually isolated. A small and variable amount of a crystalline material, m. p. 283°, was obtained and its analysis agreed with that expected for a monotoluene-*p*-sulphonate but insufficient was available for structural investigation. Later, the author was informed by Professor A. R. Todd that similar observations have been made in Cambridge.

The difficulties encountered probably arose through the reactivity of the 6-amino-group in the purine ring; consequently, attention was directed to a proof of the structure of "adenine thiomethyl pentoside" in another way.

A toluene-*p*-sulphonate of *iso*propylidene inosine was prepared by Levene and Tipson (*J. Biol. Chem.*, 1935, **111**, 313), which contained the toluene-*p*-sulphonyl residue at position 5′ since it could be substituted by an iodine atom when heated with sodium iodide in acetone (cf. Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366), and is thus 2′ : 3′-*iso*propylidene 5′-toluene-*p*-sulphonyl inosine (III).


(III.)


(IV.)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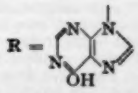

Raymond (*J. Biol. Chem.*, 1934, **107**, 85) effected substitution of a toluene-*p*-sulphonyl group by alkylthio in the sugar series by heating toluene-*p*-sulphonates and sodium or potassium derivatives of thiols in acetone at 100°. Reaction between (III) and potassium methyl sulphide under similar conditions was complicated by the formation of potassium salts which were insoluble in acetone, but this was avoided by the use of dimethylformamide as solvent; a further advantage of this solvent was that the process could be carried out at atmospheric pressure on a steam-bath. By this method (III) gave an excellent yield of 2′ : 3′-*iso*propylidene 5′-deoxy-5′-methylthioinosine (IV). Hydrolytic removal of the *iso*propylidene residue proceeded smoothly in a mixture of acetic and N-sulphuric acids to give 5′-deoxy-5′-methylthioinosine, m. p. 220—221°.

A hypoxanthine deoxymethylthiopentoside, m. p. 220·5—221·5°, was prepared by Kuhn and

Henkel (*loc. cit.*) by treatment of " adenine thiomethyl pentoside " with nitrous acid, and the author is indebted to Professor F. Weygand who reports that the synthetic substance and this hypoxanthine derivative are identical as shown by melting points, mixed melting points, specific rotations, and behaviour on paper chromatography before and after hydrolysis. Final confirmation was obtained by hydrolysis to 5-deoxy-5-methylthio-D-ribose. Reduction of this with sodium amalgam (Suziki, Ohdake, and Mori, *Biochem. Z.*, 1925, **162**, 413) yielded 5-deoxy-5-methylthio-D-ribitol, identical with that obtained in a similar way from natural " adenine thiomethyl pentoside."

Since the starting material in this synthesis, namely, inosine, was obtained by deamination of adenosine and is, therefore, 9-β-D-ribofuranosylhypoxanthine, it follows that " adenine thiomethyl pentoside " is correctly described as 9-(5-deoxy-5-methylthio-β-D-ribofuranosyl)-adenine (I).

With the experience acquired in the above synthesis, the syrupy and certainly impure toluene-*p*-sulphonation product of 2′ : 3′-*iso*propylidene adenosine was treated as above. An acetone solution of the resulting syrup slowly deposited crystalline 5′-deoxy-5′-methylthioadenosine, identical with natural " adenine thiomethyl pentoside."

As the work described in this paper was nearing completion the author was informed by Professor Weygand of related but independent investigations in progress at Heidelberg. The German workers synthesised 5′-deoxy-5′-methylthioadenosine by a route similar to that outlined above and a preliminary account of these investigations has been published jointly (Baddiley, Trauth, and Weygand, *Nature*, 1951, **167**, 359). After this had been submitted for publication Satoh and Makino described briefly the synthesis of 2′ : 3′-*iso*propylidene 5′-deoxy-5′-methylthioadenosine which they isolated as its picrate and showed to be identical with the picrate of " *iso*propylidene adenine thiomethyl pentoside " prepared from the natural nucleoside (*Nature*, 1951, **167**, 238). Similarly, they showed that synthetic 2′ : 3′-*iso*propylidene 5′-deoxy-5′-methylthioinosine picrate was identical with the picrate of the corresponding substance obtained from " hypoxanthine thiomethyl pentoside."

During our work both 2′ : 3′-*iso*propylidene adenosine and 2′ : 3′-*iso*propylidene inosine have been prepared by simpler and more reliable methods than those described by Levene and Tipson (*loc. cit.*) (see below).

Experimental.

2′ : 3′-iso*Propylidene Adenosine*.—The following method is a modification of that described by Levene and Tipson (*loc. cit.*). To a filtered solution of pure, fused zinc chloride (55 g.) in acetone [550 c.c.; previously treated with a small amount of potassium permanganate at room temperature, distilled, dried (Na_2SO_4), and redistilled] was added adenosine (19 g.; dried for 5 hours at 110°/0·1 mm. over phosphoric oxide). After boiling under reflux with the exclusion of moisture for 5 hours the slightly cloudy solution was kept at room temperature for a further 12 hours. The volume was reduced to about a third by distillation under reduced pressure and the resulting slightly viscous solution poured into a warm (40°) solution of barium hydroxide (150 g. of octahydrate) in water (*ca.* 1 l.). The mixture was cooled at once to room temperature and carbon dioxide passed in vigorously until the liquid was no longer alkaline. Zinc and barium carbonates were filtered off and washed thoroughly with alternate lots of boiling methyl alcohol and water (*ca.* 700 c.c. of each) until the washings were free from carbohydrate. The filtrate and washings were refiltered if not clear, then evaporated at <40° to about 500 c.c. During the evaporation 2′ : 3′-*iso*propylidene adenosine crystallised. After half an hour at room temperature the solid was filtered off, washed with water, and dried at 100°. A further small amount was isolated from the mother-liquors by evaporation to dryness at <40°, drying of the powdered residue at 100°, and extraction of it continuously for 5 hours with dry acetone. Evaporation of the acetone left a resin which was dissolved in a little water and made alkaline with ammonia. After storage a further amount of crystalline material was filtered off. The combined solids were dissolved in boiling 95% methyl alcohol (*ca.* 150 c.c.), and the solution was filtered and cooled. Pure 2′ : 3′-*iso*propylidene adenosine, m. p. 220°, was filtered off and dried. Evaporation of mother-liquors yielded a further small amount (total yield, 75—85%).

2′ : 3′-iso*Propylidene Inosine*.—This was prepared from inosine (9 g.) as described above but with the following modification. The aqueous solution remaining after removal of zinc and barium carbonate was evaporated to dryness at <40° and the dried residue extracted continuously with dry acetone for 5 hours. After evaporation of the acetone, the residue was dissolved in 90% methyl alcohol (200 c.c.) and made alkaline with ammonia, and a small amount of zinc removed by saturation with hydrogen sulphide, followed by filtration through silica. The filtrate was evaporated to dryness under reduced pressure and the residue recrystallised from methyl alcohol. 2′ : 3′-*iso*Propylidene inosine (5 g.) was obtained as fine needles, m. p. 267°, $[\alpha]_D^{20}$ −66·9° (*c*, 0·761 in methyl alcohol). Levene and Tipson (*loc. cit.*) record m. p. 240—245° and $[\alpha]_D^{24}$ −69·2° (*c*, 0·578 in methyl alcohol), but the discrepancy in m. p. is probably explained by the failure of these authors to remove zinc salts from their material.

Reaction between 2′ : 3′-iso*Propylidene Adenosine and Toluene*-p-*sulphonyl Chloride*.—A solution of toluene-*p*-sulphonyl chloride (0·68 g.) in dry benzene (2 c.c.) was added dropwise to a solution of *iso*propylidene adenosine (1·0 g.; dried for 1 hour at 120°/0·1 mm.) in anhydrous pyridine (100 c.c.),

cooled to −10°. After 3 days at room temperature water (10 c.c.) was added and the solvent removed under reduced pressure. The residue was dissolved in chloroform (50 c.c.) and washed successively with small amounts of ice-cold dilute sulphuric acid, sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The resulting resin was dissolved in alcohol–chloroform (1 : 1), and the solution passed through a short column of alumina. After the column had been washed with alcohol until free from carbohydrate, eluate and washings were evaporated to dryness under reduced pressure. The residue was dissolved in a little alcohol and made just cloudy with *cyclo*hexane. Crystals of unchanged *iso*propylidene adenosine usually appeared at this point but occasionally these were mixed with another crystalline substance. The two compounds were separated by fractional crystallisation from alcohol–*cyclo*hexane. The *toluene-p-sulphonyl* derivative, m. p. 283° (decomp.), was recrystallised from alcohol–*cyclo*hexane (Found: C, 51·9; H, 4·9; N, 15·3; S, 6·9. $C_{20}H_{23}O_4N_5S$ requires C, 52·0; H, 5·0; N, 15·2; S, 6·9%).

2′ : 3′-iso*Propylidene 5′-Deoxy-5′-methylthioinosine*.—To a solution of 2′ : 3′-*iso*propylidene 5′-toluene-*p*-sulphonyl inosine (1·0 g.) in anhydrous dimethylformamide (15 c.c.) was added dry potassium methyl sulphide (1 g.; prepared from a solution of methanethiol in ether and powdered potassium). Suspended solid dissolved on warming. The solution was heated on a steam-bath with exclusion of moisture for 2 hours, cooled in ice, diluted with ice-water (30 c.c.), and neutralised with cold dilute sulphuric acid. The precipitated solid was dissolved in chloroform, and the chloroform solution separated, washed with a little water, and evaporated to dryness under reduced pressure. The crystalline residue was recrystallised from chloroform–ether. The *methylthio*-derivative (0·65 g., 90%) crystallised in prisms, m. p. 234°, $[\alpha]_D^{25}$ −16·5° (*c*, 3·29 in chloroform) (Found: C, 49·8; H, 5·4; N, 16·0; S, 9·3. $C_{14}H_{18}O_4N_4S$ requires C, 49·7; H, 5·3; N, 16·5; S, 9·5%).

5′-Deoxy-5′-methylthioinosine.—A solution of the *iso*propylidene compound (IV) (0·2 g.) in acetic acid (10 c.c.) and N-sulphuric acid (10 c.c.) was kept at room temperature for 48 hours. The sulphuric acid was neutralised with the calculated amount of barium hydroxide solution, barium sulphate was removed by centrifugation and washed with water, and the supernatant liquid and washings were evaporated to dryness at <40°. The residue was dissolved in water (25 c.c.), filtered through Supercel silica, and evaporated to dryness again at <40°. The crystalline product (0·16 g., 92%) was recrystallised from a small amount of hot water. *5′-Deoxy-5′-methylthioinosine* crystallised as fine needles, m. p. 220—221° (Found: C, 44·3; H, 4·6; N, 18·5; S, 10·6. $C_{11}H_{14}O_4N_4S$ requires C, 44·3; H, 4·7; N, 18·8; S, 10·7%).

(Based on a report by Professor F. Weygand.) The above compound and " hypoxanthine thiomethyl pentoside," after recrystallisation from water and drying ($CaCl_2$), had m. p. 221—222°, undepressed on admixture. Microscopic examination of samples showed the presence in each of prisms and fine needles, the melting points and specific rotations of which are tabulated. The mixed m. p. of samples

	$[\alpha]_D^{20\cdot1}$ (*c*, 0·17 in pyridine).	Recryst. from water; m. p. (Köfler block).	Recryst. from wet butanol; m. p. (Köfler block).
5′-Deoxy-5′-methylthioinosine	−24·1° ± 2°	Prisms 223—224°	223—224°
		Needles 226·5°	226·5°
" Hypoxanthine thiomethyl pentoside "	−22·5° ± 2°	Prisms 224°	222—223°
		Needles 227°	226·5°

recrystallised from water was 227° and that of samples recrystallised from wet butanol was 225—226°. Hydrolysis of the synthetic substance with 5% sulphuric acid and reduction with sodium amalgam (Suziki, Ohdake, and Mori, *loc. cit.*) gave 5-deoxy-5-methylthio-D-ribitol, m. p. 118—119° undepressed when mixed with the deoxymethylthiopentitol, m. p. 118—119°, obtained from " adenine thiomethyl pentoside."

5′-Deoxy-5′-methylthioadenosine.—The resin obtained by toluene-*p*-sulphonation of *iso*propylidene adenosine (4·0 g.) by the above-mentioned method was dissolved in anhydrous dimethylformamide (*ca.* 30 c.c.), and dry potassium methyl sulphide (2·0 g.) was added. The mixture was heated at 100° for 2 hours, cooled, and poured into water, and the crude product extracted with three lots of chloroform. Evaporation of the chloroform solution left a reddish-brown resin. This was dissolved in acetic acid (25 c.c.) and N-sulphuric acid (25 c.c.) added. After 2 days at room temperature the acid was neutralised with the calculated amount of barium hydroxide solution, and barium sulphate removed by centrifugation. The precipitate was washed twice with water, and the combined supernatant liquids were evaporated to dryness under reduced pressure. The resulting syrup was dissolved in a little acetone, adjusted to pH 7 with ammonia, and set aside at room temperature. After some time crystals appeared and during 3—4 weeks small crops were removed by filtration. The combined solids (*ca.* 400 mg.) were recrystallised from water and had m. p. 205°, unaltered by recrystallisation from water or wet butanol (Found: C, 44·5; H, 5·0; N, 23·6. Calc. for $C_{11}H_{13}O_3N_5S$: C, 44·4; H, 5·1; N, 23·5%).

Comparison of the synthetic nucleoside with " adenine thiomethyl pentoside " from yeast was carried out by Professor Weygand. The synthetic substance melted at 212° (Köfler block) and was undepressed when mixed with a sample of the natural nucleoside, m. p. 212—213°. On paper chromatography in butanol–water the substances were indistinguishable (R_F 0·58).

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The Lister Institute of Preventive Medicine,
London, S.W.1.

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301. *The Oxides of Uranium. Part II.* The Binary System* UO_2–CaO.

By K. B. Alberman, R. C. Blakey, and J. S. Anderson.

The phase diagram of the system CaO–UO_2 has been investigated in the temperature range 1650—2300° c. The eutectic temperature is 2080° ± 20°, and the eutectic composition about 45 moles % of UO_2 and 55 moles % of CaO. The CaO takes no detectable amount of UO_2 into solid solution, but the UO_2 forms solid solutions, with defective fluorite structure, the saturated solid solution containing 47 mols. % of CaO at the eutectic temperature. The concentration of CaO in the saturated solid solution decreases with falling temperatures, down to 20 moles % at 1650°. At 1750° and below, two compounds are formed: Ca_2UO_4 (= $2CaO,UO_2$), a tetragonal double oxide of unknown structure; and $CaUO_3$ (= CaO,UO_2), having a cubic cell with $a = 10{\cdot}727 \pm 0{\cdot}002$ *kX*. The structure of the latter is equivalent to the Type-C rare-earth oxide structure, with $Ca^{2+} + U^{4+}$ replacing $2M^{3+}$.

Studies of binary oxide systems have brought to light a number of interesting regularities in the field of crystal chemistry, but few systems involving two species of large cations appear to have been studied hitherto. Uranium dioxide crystallises with the fluorite structure (a = 5·457 A.), the interatomic distance U–O being 2·363 A.; in calcium oxide the distance Ca–O is 2·398 A. The relatively large U^{4+} and Ca^{2+} cations are thus of closely similar effective radius, and it might be expected *a priori* that the system UO_2–CaO would display the formation of anomalous mixed crystals and of intermediate phases with structures not encountered in binary systems involving smaller cations. The work now described has shown that this is, indeed, the case, and it brings out clearly the trend from an ordered to a random arrangement of defect structures as the temperature is raised.

Uranium dioxide and lime are highly refractory, with melting points approximately 2700° and 2500°, respectively. The study of their phase equilibrium is therefore essentially a problem of high-temperature techniques. The literature contains relatively few equilibrium studies between such refractory substances. Above about 1850° the phase diagram for CaO–UO_2 found from the present work resembles that constructed by Zhirnova (*J. Appl. Chem. U.S.S.R.*, 1939, **12**, 1279) from fragmentary data for the ZrO_2–MgO system. The eutectic temperature is about 2080°, and a few temperatures on the solidus curve of the UO_2 phase were determined directly, at temperatures up to 2250°. The liquidus curves and the uppermost portions of the solidus curves can, however, be only sketched in the phase diagram in their probable positions. Direct measurements in those regions of the phase diagram lying at temperatures above 2300° would, indeed, involve considerable experimental difficulty.

Experimental.

All specimens were fired in a small tungsten-spiral vacuum furnace, described in detail elsewhere (Alberman, *J. Sci. Instr.*, 1950, 280). This furnished temperatures up to approximately 2500° within a useful volume of about 20 c.c., and with a maximum energy consumption of about 1200 watts. The energy consumption at high temperatures was shown by direct calibration (Alberman, *loc. cit.*) to be strictly proportional to T^4, and in the present work all temperatures were measured by the power input to the furnace. The ambient pressure was maintained at $<10^{-3}$ mm. by an efficient pumping system.

The oxides used as starting materials were "AnalaR" calcium oxide, and a very pure grade of uranium dioxide. Mixtures were made up synthetically to accurately known compositions. For this purpose, the lime was brought to constant weight at 800° in a platinum crucible, or in some cases was "dead burned" at considerably higher temperatures, and then finely ground with the appropriate quantity of uranium dioxide. The mixtures were pressed (under 15 tons/sq. cm.) into pellets of ¼" diam. and of various lengths, suited to their purpose. This was done immediately before firing as absorption of moisture brought about disintegration. The pellets formed in this way had sufficient mechanical strength for careful handling with forceps.

Pellets for *X*-ray analysis were made about 1 in. long, so that when they were standing on the tantalum base of the furnace enclosure, the topmost ¼" was in the centre of the heated zone (Fig. 1). After being heated at temperatures between 1650° and 2100° for various times, the top portion of the pellet was broken away, ground in an agate mortar, and loaded into thin-walled Pyrex *X*-ray capillaries. Contamination by diffusion of tantalum from the base plate (see below) was thereby minimised. Two-phase materials, containing free lime as one solid phase, were leached with ammonium chloride solution, in order to dissolve the lime under nearly neutral conditions, thereby isolating the second phase for *X*-ray analysis.

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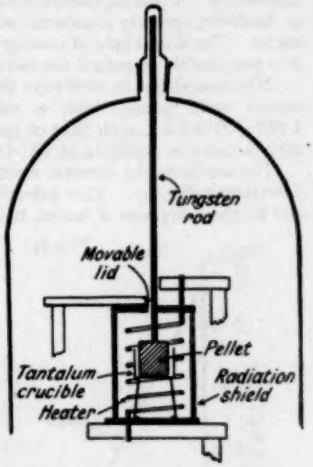
Pellets for thermal analysis were made about 1 cm. long, and were place in tantalum crucibles (7/16" diam., ¼" deep) made by deep-drawing 0·010" tantalum sheet. The crucibles were suspended in the centre of the heated zone by a light spot-welded framework of tantalum and tungsten. Melting points were then determined directly by a simple technique. A long rod of tungsten rested on the top of the pellet, with its upper end projecting into a length of narrow tubing attached to the bell-jar which covered the furnace assembly (Fig. 1). The top end of the tungsten rod was observed through a cathetometer as the temperature of the furnace was gradually raised. When liquefaction commened, the rod sank through the contents of the tantalum crucible, at a rate depending on the proportions of liquid phase and unmelted solid. The m. p. was then determined from the power input at the commencement of fusion; the temperature scale was calibrated both by optical pyrometry and by determining a series of melting points between those of nickel (1455°) and iridium (2440°). The measurements were quite reproducible, seven measurements of the eutectic temperature, on compositions covering the full width of the equilibrium diagram, giving a value of 2080° with a standard deviation less than 20°.

FIG. 1.



X-Ray Measurements.—Diffraction patterns were taken on a 9-cm. Unicam camera, with filtered copper-$K\alpha$ radiation. Measurements of cell dimensions were extrapolated by Nelson and Riley's method (*Proc. Physical Soc.*, 1945, **57**, 160), the value of a_{100} at $\theta = 90°$ being obtained by combining the ten lines of highest diffraction angle recorded on the film, by the method of least squares. The values recorded are probably reliable to $\pm 0{\cdot}001$ *kX*.

Metallographic Examination.—This was used primarily to locate the eutectic composition, since the method of thermal analysis employed was not capable of fixing temperatures on the liquidus curve, but only gave the m. p. of the eutectic over the whole range of its existence. Portions of pellets from the m. p. experiments were mounted in Bakelite, and polished on a carborundum wheel. On examination under a metallurgical microscope, particles of primary phase could be seen embedded in a continuous matrix of eutectic, the appearance being similar to that of duplex metallic systems. On the lime-rich side of the eutectic, the primary phase (CaO) could be removed by etching with concentrated hydrochloric acid, leaving a network of eutectic. A specimen with 55 moles % of CaO and 45 moles % of UO_3 melted very sharply and showed no crystals of a primary phase under the microscope. It was concluded that this mixture was close to the eutectic composition.

Chemical Analysis.—The gross composition of all mixtures was adjusted synthetically to cover the requisite range, and the compositions of the saturated uranium dioxide solid solution phases were determined with considerable accuracy by the *X*-ray data. The validity of this method was checked, and the composition of the compounds in the system determined by direct chemical analysis. Two-phase products, consisting of lime + solid solution or lime + compound, were exhaustively leached of lime by means of ammonium chloride solution, which did not attack the solid phases containing uranium dioxide. The residue, for analysis, was dissolved in 50% nitric acid + hydrogen peroxide or by fusion with potassium hydrogen sulphate. Calcium was first precipitated as oxalate, and uranium then determined by precipitation with tannin (cf. Powell and Schoeller, "Analysis of Minerals and Ores of the Rarer Elements"). The tannin precipitates were tested for tantalum (and tungsten, which was not, however, detected in more than trace amounts) as described by Powell and Schoeller.

Side Reactions and Chemical Contamination.—The heated tantalum and tungsten parts of the furnace act as efficient "getters," and we have some evidence that the oxygen pressure within the heated enclosure is maintained at less than 10^{-4} mm. The dissociation pressure of most, even the more refractory, oxides becomes of this order of magnitude at temperatures between 2000° and 2500°, and we have, in fact, observed the decomposition of all except the most stable oxides (*e.g.*, ThO_2) under the conditions attainable in our vacuum furnace. In particular, at the point of contact with a tantalum crucible or tantalum floor, direct displacement of more volatile metals (*e.g.*, Ca, and even Th) can occur, leading to the entry of tantalum into the system (*e.g.*, with the formation of ternary solid solutions). In the absence of a liquid phase, diffusion of tantalum into the pellets was not excessively rapid, and the upper parts of pellets, used for *X*-ray analysis, were free from tantalum. With the occurrence of eutectic melting, reaction was rapid, and the interior of the bell-jar was rapidly covered with condensed calcium; in these circumstances as much as 14% of tantalum dioxide was found in the melt after complete fusion. Eutectic temperatures were, however, taken from the first signs of melting, and it is believed that no considerable errors were introduced from this source.

Results and Discussion.

The UO_2–CaO *Mixed-crystal Phase and the Melting Equilibria.*—The addition of lime to uranium dioxide gives rise to a solid solution phase, with fluorite structure, having a considerable breadth of composition at 1900—2100°. The cubic unit cell shrinks quite regularly as $U^{4+} + 2O^{2-}$ is progressively replaced (see below) by $Ca^{2+} + O^{2-} + \square O$, where $\square O$ denotes a vacant oxygen site. The lattice parameter a varies linearly with the molar fraction of lime, and

can therefore be used to determine the limiting composition of the solid solution phase, in material of duplex structure, richer in lime (Fig. 2). The compositions of the saturated solid solution at 1950° and at the eutectic temperature (2080°) were determined in this way as 43 and 47 moles % of lime. The composition of the saturated solid solution at 1950° was determined analytically as 40 moles %. Specimens that had been melted were invariably contaminated rather heavily with tantalum; analytical figures obtained on such material are therefore not significant. The composition of the limiting solid solution determined from *X*-ray measurements is, however, entirely consistent with the experimental evidence for the position of the solidus curve. The initial rate of cooling of a sample from temperatures around 2000° was so high that it is permissible to regard the switching off of the furnace as equivalent to a quenching process.

Mixtures richer in lime than the saturated solid solution showed the presence of lime as the second solid phase, with a cell dimension identical, within our limits of error ($a = 4{\cdot}797 \pm 0{\cdot}001$ A.), with that of pure lime. It may be concluded that the lime phase does not take detectable amounts of U^{4+} cations into solid solution.

The limits of the eutectic melting range were thus fixed, and the eutectic temperature was determined directly. This eutectic composition was shown, by the metallographic examination and by the sharpness of fusion, to be close to 45 moles % of uranium dioxide. The m. p.s of the

FIG. 2.

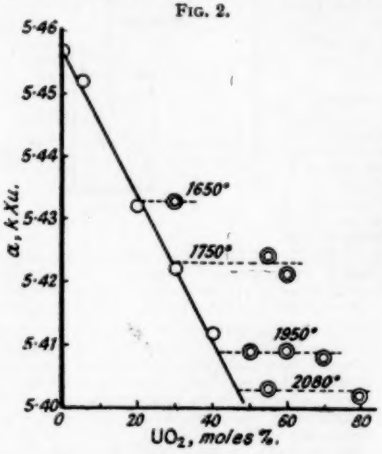
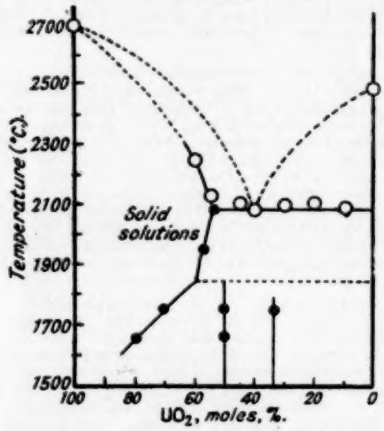


FIG. 3.



unsaturated uranium dioxide solid solutions rose very steeply with increasing dioxide content; it was proved that the mixture with 70 moles % of this oxide must melt well above 2300°. Hence the solidus curve could not be followed directly beyond the composition 60 moles % UO_2, 40 moles % CaO, but the data obtained experimentally are sufficient to enable the remainder of the equilibrium diagram to be filled in with considerable confidence (Fig. 3).

Intermediate Phases.—The tolerance of the uranium dioxide fluorite structure for lattice defects diminishes markedly as the temperature is reduced; the saturation concentration of calcium oxide decreased and the cell dimension of the uranium dioxide phase increased accordingly when materials with 50—70 moles % of the dioxide were annealed at temperatures below 2090°. The change in a was particularly marked at 1750° and 1650° (Table I). At the same time, in mixtures richer in lime (*e.g.*, 30 moles % UO_2 + 70 moles % CaO) a new phase appeared, having a diffraction pattern which could be largely indexed in terms of a fluorite cell much *smaller* than that found even for the solid solutions richest in lime. The formation of the new phase was not observed in mixtures with 50 moles % of uranium dioxide, and it was therefore first interpreted as a double oxide nCaO,UO_2, where $n > 1$. However, when specimens of the 70/30 and 80/20 CaO–UO_2 mixtures, well annealed at 1750°, were exhaustively leached with ammonium chloride solution, the resulting product was found by analysis to be CaO,UO_2 (Found : CaO, 17·30; UO_2, 83·16. Calc. : CaO, 17·19; UO_2, 82·81%), and gave a diffraction pattern which could be completely indexed in terms of the rare-earth " Type-C " structure, with $a = 10{\cdot}727 \pm 0{\cdot}002$ A., 16 molecules of $CaUO_3$ per unit cell (Table III); hence in this double oxide, $Ca^{2+} + U^{4+}$ are substituted for the $2M^{3+}$ cations of the rare-earth oxides. That the

TABLE I.

UO_3, moles, %.	M. p. (° c.).	Cell dimensions. a (2080° c.). UO_2.	a (1950° c.). UO_2.	a (1950° c.). CaO.	a (1750° c.). UO_2.	a (1650° c.). UO_2.
100	2700	—	5·4573	—	—	—
94·6	—	—	5·4516	—	—	—
80	—	—	5·4317	—	—	—
70	2300	—	5·4215	—	—	5·4329
60	2250	—	5·4120	—	—	—
55	2120	—	—	—	—	—
50	2060	5·4028	5·4093	—	—	—
45	2100	—	—	—	5·4243	—
40	2080	—	5·4087	—	5·4214	—
30	2090	—	5·4083	—	—	—
20	2100	5·4023	—	—	Polyphase region	—
10	2090	—	—	4·7962	Polyphase region	—
5	—	—	—	4·7971	—	—
0	2500	—	—	4·7977	—	—

TABLE II.

		2080°	1950°	1750°	1650°
Temp.					
Composition of saturated solution	CaO, moles %	47	43	29	20
	UO_3, moles %	53	57	71	80

TABLE III.

Diffraction pattern of $CaUO_3$.

θ.	d (uncorr.), A.	*hkl*.	d, calc.	θ.	d (uncorr.), A.	*hkl*.	d, calc.
9·17°	4·831	Compound C	—	39·92°	1·199	840	1·199
10·66	4·158	(211 or Compound C)	4·379	41·13	1·170	842	1·173
				41·92	1·152	921, 761, 655	1·157
14·31	3·112	222	3·097	43·54	1·117	930	1·131
15·14	2·948	Compound C	—			932	1·107
16·63	2·689	400	2·682	44·72	1·094	844	1·095
17·93	2·499	411, 330	2·528	48·17	1·033	1022, 666	1·033
18·47	2·430	Compound C	—	49·25	1·0160	1031, 952	1·023
18·95	2·370	420	2·398	50·62	0·9958	1040, 864	0·9959
21·74	2·078	431, 510	2·103	51·63	0·9816	1033, 961	0·9875
23·86	1·902	440	1·897	52·58	0·9690	1110, 954	0·9711
24·40	1·863	433, 530	1·840	53·44	0·9583	1121, 1051	0·9556
26·72	1·712	532, 611	1·740	54·17	0·9493	880	0·9481
27·32	1·677	602	1·696	55·06	0·9388	970, 1130	0·9407
28·44	1·617	622	1·617	57·15	0·9162	1060, 866	0·9198
29·32	1·572	631	1·582	58·07	0·9069	1062	0·9066
29·83	1·547	444	1·548	59·41	0·8940	1200, 884	0·8939
31·10	1·490	640	1·488	63·91	0·8569	1073	0·8533
32·24	1·443	721, 633	1·460	65·40	0·8465	1240	0·8480
		642	1·434	68·42	0·8277	10·82	0·8276
33·29	1·403	730	1·409	70·01	0·8190	1066	0·8178
35·80	1·316	811, 741	1·320	72·04	0·8091	12·44	0·8085
37·60	1·261	822, 660	1·264	73·31	0·8035	1330,994	0·8039
38·75	1·230	662	1·230	79·72	0·7822	1341, 1174	0·7865
39·45	1·211	752	1·214	81·37	0·7785	1093	0·7781

$a = 10·727 \pm 0·002$.

formation of $CaUO_3$ is observed only in mixtures containing an excess of free lime is explicable if the double oxide is formed by the phase reaction

$$\underset{\text{(solid solution phase)}}{Ca_{(1-x)}U_xO_{(1+x)}} + (2x-1)CaO \longrightarrow \underset{\text{(Type-C phase)}}{xCaUO_3} \quad . \quad . \quad . \quad . \quad . \quad (1)$$

occurring at the interface between crystals of lime and of the solid solution. The *X*-ray measurements are summarised in Table II. The type-C oxide structure contains two sets of cation positions: 8 cations on Wyckoff's 8 (*e*) ($\pm$ ¼ ¼ ¼ and its permutations), and 24 cations on 24 (*e*) ($\pm$ *u*0¼ with $u = ca. -0·030$). Hence $16Ca^{2+}$ and $16U^{4+}$ could be accommodated (*a*) with Ca^{2+} and U^{4+} distributed statistically over all positions, (*b*) with $8U^{4+}$ on 8(*e*) and $8U^{4+} + 16Ca^{2+}$ on 24(*e*), or (*c*) with $8Ca^{2+}$ on 8(*e*) and $16U^{4+} + 8Ca^{2+}$ on 24(*e*). These alternatives lead to different relative intensities for certain "non-fluorite" reflections, though only a few lines are available for comparison and not obscured by coincidences. The observed intensity data are in best accord with alternative (*a*) *i.e.*, random distribution of Ca^{2+} and U^{4+} over all cation sites.

In attempting to identify the double oxide (later proved to be $CaUO_3$) by bracketing the compositions $3CaO,UO_3$, etc., it was found that a second intermediate phase, phase C, appeared on prolonged annealing of 80/20 and 90/10 CaO–UO_3 mixtures, being formed apparently by a second phase reaction between $CaUO_3$ and CaO. This was finally isolated by the same method as used for isolation of $CaUO_3$, and although it remained a little uncertain whether the product was, in fact, still contaminated with $CaUO_3$, the analytical results indicated that the second compound was $2CaO,UO_3$ (= Ca_2UO_4). The diffraction pattern indicated a tetragonal cell with at least one rather large dimension; the measurements, listed in Table IV, could be quite well indexed in terms of a cell with $a = 16{\cdot}760$, $c = 9{\cdot}208$ *kX*, $c/a = 0{\cdot}549$, which could contain 32 molecules of Ca_2UO_4 in conformity with Zachariasen's data for the spatial requirements of Ca^{2+}, O^{2-}, and U^{4+}.

TABLE IV.

Diffraction pattern of Ca_2UO_4.

$a = 16{\cdot}760$; $c = 9{\cdot}208$ A.; $c/a = 0{\cdot}549$.

θ.	d (uncorr.).	*hkl*.	d, calc.	Intensity.	θ.	d (uncorr.).	*hkl*.	d, calc.	Intensity.
9·21°	4·809	301	4·778	w	30·91	1·498	1101	1·503	vvw
9·45	4·688	320	4·647	w			545	1·506	
10·73	4·134	321	4·148	ms	31·45	1·475	880	1·481	w
		400	4·188		32·01	1·452	705	1·460	vvw
14·92	2·989	332	2·997	w			326	1·457	
15·16	2·943	440	2·963	s	33·26	1·403	882	1·410	vvw
15·55	2·871	530	2·875	w	33·74	1·386	516	1·390	vvw
		203	2·882		35·41	1·328	1212	1·332	vvw
17·72	2·529	621	2·547	vw			883	1·334	
18·08	2·480	630	2·499	vw	35·70	1·319	1240	1·325	vvw
		442	2·491		36·15	1·305	1080	1·309	vw
18·47	2·429	522	2·439	vw			905	1·309	
18·91	2·375	602	2·388	vw	36·69	1·288	925	1·294	vw
21·71	2·081	800	2·095	m			706	1·292	
23·94	1·897	802	1·907	vw	37·37	1·268	1242, 1171	1·273	vw
24·36	1·866	840	1·874	w	38·17	1·245	1260, 945	1·249	w
24·69	1·843	524	1·851	vw	39·10	1·220	826, 507	1·224	vw
26·53	1·723	803	1·730	m	40·76	1·179	1224	1·182	w
		544	1·728		41·57	1·160	1055	1·163	vw
27·22	1·683	770	1·693	m	42·10	1·148	008, 1440	1·151	vw
28·47	1·615	724	1·628	vw	42·79	1·133	776	1·137	vw
28·86	1·595	951	1·603	vvw	43·27	1·123	1371	1·126	w
		843	1·599		44·23	1·099	1372	1·102	vw

The two intermediate compound phases were not formed in any experiments carried out at 1900—1950°, and so must decompose between 1750° and 1950°. From the trend in the compositions of the limiting UO_3 solid solutions it would appear that the upper limit of occurrence of the phase reaction (1) is somewhere about 1850° ± 50° (giving the final phase diagram shown in Fig. 2).

The compound $CaUO_3$ appears to be the first example of a double oxide, ABO_3, crystallising with the Type-C rare-earth oxide structure. It thus extends our knowledge of the systematics of a class of compound which clearly reflects the influence of ionic radii upon the stability of alternative crystal structures. The simple oxides A_2O_3 formed by small cations ($r_A : r_O < 0{\cdot}60$) crystallise with the corundum structure, and double oxides ABO_3 for which $r_A : r_O$ and $r_B : r_O$ are both $< 0{\cdot}6$ assume the related ilmenite structure. Examples are $FeTiO_3$, $LiNbO_3$. Larger tervalent cations give rise to A_2O_3 oxides with the cubic Type-C structure ($0{\cdot}6 < r_A : r_O < 0{\cdot}8$) or the hexagonal type-A structure ($r_A : r_O > 0{\cdot}8$). ABO_3 double oxides described hitherto, containing at least one fairly large cation, have all had the perovskite structure, which has a remarkable range of stability; it includes double oxides with radius ratios as diverse as those of $YAlO_3$ ($r_Y : r_O = 0{\cdot}67$, $r_{Al} : r_O = 0{\cdot}36$), $LaAlO_3$ ($r_{La} : r_O = 0{\cdot}82$, $r_{Al} : r_O = 0{\cdot}36$), and $BaCeO_3$ ($r_{Ba} : r_O = 0{\cdot}96$, $r_{Ce} : r_O = 0{\cdot}72$). It would appear, therefore, that the $CaUO_3$ type, related to the type-C structure in the same way that the ilmenite type is derived from the corundum structure, is probably formed only where the cations A and B are not merely appropriate, but also similar in size.

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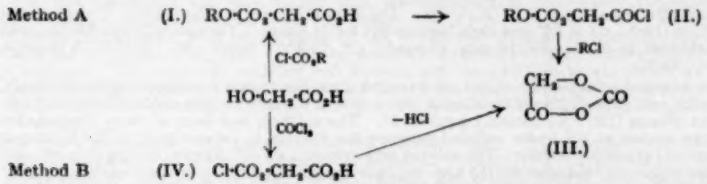
302. *Anhydrocarboxy-derivatives of Hydroxy- and Mercapto-acids.*

By W. H. Davies.

Anhydrocarboxy-derivatives have been prepared from glycollic, α-mercaptoacetic, lactic, mandelic, and salicylic acids by reaction with carbonyl chloride. These compounds react vigorously with water and carbon dioxide is eliminated. The first four react with aniline with evolution of carbon dioxide to give anilides: anhydro-*O*-carboxysalicylic acid with aniline gives *o*-carboxyphenyl phenylcarbamate. The anhydrocarboxy-compounds react with aromatic hydrocarbons under Friedel–Crafts conditions to give ketones.

Although anhydro-*N*-carboxyamino-acids (oxazolid-2 : 5-diones) and anhydro-*O*-carboxysalicylic acid (benzo-1 : 3-dioxen-2 : 4-dione) have been known for many years, the corresponding derivatives from α-hydroxy-acids [1 : 3-dioxolan-2 : 4-diones (III)] and α-mercapto-acids (1 : 3-oxathiolan-2 : 5-diones) have not been reported. These have now been obtained by reaction of the appropriate acids with carbonyl chloride.*

Attempts were made to prepare anhydro-*O*-carboxyglycollic acid (III) from the carbonate (I) by method A, analogous to Bergmann's preparation of anhydro-*N*-carboxyamino-acids (*Ber.*, 1932, **65**, 1194). Carbonato-esters (I) were prepared by reaction of glycollic acid with chloroformates. The benzyl ester, which was obtained only in poor yield, was rather unstable, and the ethyl ester was therefore prepared. This was converted into the ester chloride (II; R = Et) which could not be cyclised: it was recovered unchanged after being heated to 180°, and heating in the presence of a trace of pyridine caused decomposition to carbon dioxide and a black solid. This method of approach was therefore discontinued, and Method B, analogous to the patented preparation of anhydro-*N*-carboxyamino-acids (B.P. 646,033), was examined.



Preliminary work showed that dioxan was a very suitable solvent for the interaction of glycollic acid with carbonyl chloride. From a series of experiments with glycollic acid in this solvent, it was found that a large excess of carbonyl chloride and a long reaction time at room temperature minimised the formation of the carbonate $CO(O{\cdot}CH_2{\cdot}CO_2H)_2$ and helped conversion into the chloroformate (IV). The cyclisation of (IV) to (III) was effected by removing the solvent at low temperature and heating the residual oil at 60°/20 mm. for two hours. Longer heating under these conditions, though not improving the yield of (III), reduced the ionisable halogen in the crude product: this probably indicates slow removal of some diacid chloride, $Cl{\cdot}CO_2{\cdot}CH_2{\cdot}COCl$. By a similar method, lactic, mandelic, and α-mercaptoacetic acids were converted into their anhydrocarboxy-derivatives. In all these cases, poorer yields were obtained when salts of the acids were used in place of the free acids, though anhydro-*O*-carboxysalicylic acid was best prepared by Dupont's method of reaction of the disodium salt of salicylic acid in toluene with carbonyl chloride (B.P. 426,243).

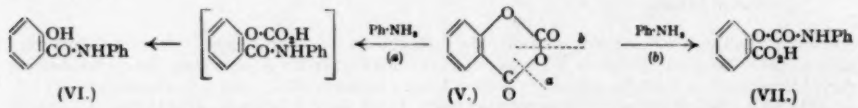
The purity of the crude anhydrocarboxy-acids was found approximately by treating samples with water and observing the loss in weight due to evolution of carbon dioxide. Although this method was not accurate—even pure anhydro-*O*-carboxyglycollic acid gave low results, and by-products such as carbonates might also give carbon dioxide on treatment with water—the results were reasonably consistent and tallied with the yield of anilide obtained by treatment with aniline.

The anhydrocarboxy-derivatives were easily purified by crystallisation from dry, low-boiling solvents. The stability of the products varied with the particular acid used. When heated at 100° for 18 hours, anhydro-*O*-carboxyglycollic acid lost carbon dioxide to give the polymer

* Patent protection pending.

H·[O·CH_2·CO]$_n$·X, whereas the lactic acid derivative after such treatment was recovered largely unchanged. (The HX in such polymers is presumably provided by adventitious traces of water or acid.) The anhydrocarboxy-derivatives of α-substituted acids also decomposed with evolution of carbon dioxide upon reaction with water or amines : with limited amounts of the reagent, polymeric material was formed but with excess of water or aniline the products were mainly monomeric, HO(or HS)·CHR·COX.

Anhydro-*O*-carboxysalicylic acid (V), with its six-membered heterocyclic ring, liberated carbon dioxide on heating or on treatment with water but not on treatment with excess of aniline. The product formed was the aniline salt of *o*-carboxyphenyl phenylcarbamate (VII), indicating that fission occurred at (*b*) in (V) and not at (*a*), which would have yielded salicylanilide (VI).



(VI.) (V.) (VII.)

Statham (*J.*, 1951, 213) has shown that anhydro-*N*-carboxyamino-acids react with, *e.g.*, benzene under Friedel–Crafts conditions to give α-amino-ketones. It has now been found that in the same way anhydro-*O*-carboxyglycollic acid reacts with benzene or acenaphthene to give an α-hydroxyacetyl derivative, and anhydro-*O*-carboxysalicylic acid reacts with benzene to give *o*-hydroxybenzophenone.

Experimental.

Preparation of Carbonato-glycollic Acid Derivatives.—(a) O-*Carbethoxyglycollic acid* (I; R = Et). This was prepared by Fischer and Fischer's method (*Ber.*, 1914, **47**, 771) for the corresponding methyl ester, ethyl chloroformate being used in place of methyl chloroformate. The *acid*, b. p. 99—100°/0·12 mm., m. p. 46—48°, was hygroscopic (Found : C, 40·1; H, 5·65%; equiv., 152. $C_5H_8O_5$ requires C, 40·5; H, 5·4%; equiv., 148).

(b) O-*Carbethoxyglycollyl chloride* (II; R = Et). The acid (18·3 g.) in ether (10 c.c.) was treated with thionyl chloride (18·3 c.c.) at 35° and then kept at 50° for 1½ hours. The product was fractionated to give the *acid chloride*, b. p. 88—90°/18 mm. (Found : Cl′, 21·4%; equiv., 83. $C_5H_7O_4Cl$ requires Cl′, 21·3%; equiv., 83·2).

Preparation of Anhydrocarboxy-acids.—(a) 1 : 3-*Dioxolan*-2 : 4-*dione* (*anhydro*-O-*carboxyglycollic acid*). A solution of glycollic acid (228 g., 3 mols.) in dioxan (840 c.c.) was run into a solution of carbonyl chloride (900 g., 9 mols.) in dioxan (720 c.c.) during 1 hour at 5°. The solution was kept at room temperature for 4 days and then heated at 30° under reduced pressure for 4 hours to remove part of the hydrogen chloride and excess of carbonyl chloride. The solvent was removed at 40°/20 mm. during 5 hours, and the residual fuming yellow oil heated at 60°/15 mm. for 5½ hours, giving crude *anhydro*-O-*carboxyglycollic acid* as a brown oil (337 g.). Analysis indicated that it was about 67% pure (by CO_2-loss in water) and contained Cl′, 3·2%. (The halogen probably indicates the presence of Cl·CO·CH_2·COCl.) Crystallisation from an equal bulk of ether with good cooling gave the pure anhydro-acid, m. p. 18° (Found : C, 35·45; H, 2·35. $C_3H_2O_4$ requires C, 35·3; H, 2·0%). It was distilled in small amounts though with considerable decomposition, b. p. 49°/0·1 mm.

(b) 1 : 3-*Oxathiolan*-2 : 5-*dione* [*anhydro*(*carboxythio*)*acetic acid*]. This was prepared as in (a) from α-mercaptoacetic acid (13·8 g., 0·15 mol.) and carbonyl chloride (30 g., 0·3 mol.), the final cyclisation being effected during 3 hours at 60°/15 mm. A solution of the crude oil in ethyl acetate (15 c.c.) cooled below 0° gave *anhydro*(*carboxythio*)*acetic acid*, m. p. 68—70° (decomp.) (Found : C, 30·45; H, 2·0. $C_3H_2O_3S$ requires C, 30·5; H, 1·7%).

(c) 5-*Methyl*-1 : 3-*dioxolan*-2 : 4-*dione* (*anhydro*-O-*carboxylactic acid*). This was prepared from freshly distilled lactic acid (45 g., 0·52 mol.) and carbonyl chloride (155 g., 1·53 mols.) in dioxan as in the previous preparations. The final cyclisation was not completed during 2 hours at 60°/15 mm. and continued heating for a further hour at 65°/15 mm. was necessary. The crude oil (69% material, containing Cl′, 1·9%) was twice crystallised from ether (70 c.c.) with good cooling to give *anhydro*-O-*carboxylactic acid* (23·5 g., 40·5%), m. p. 27—28° (Found : C, 41·25; H, 3·4; CO_2-loss in water, 37·4. $C_4H_4O_4$ requires C, 41·4; H, 3·45; CO_2-loss, 37·8%). It distilled, without appreciable decomposition, at 93°/15 mm.

(d) 5-*Phenyl*-1 : 3-*dioxolan*-2 : 4-*dione* (*anhydro*-O-*carboxymandelic acid*). A solution of mandelic acid (10·1 g., 0·065 mol.) was treated with carbonyl chloride (10 g., 0·1 mol.) in dioxan as in the previous preparation. After 4 days, the solvent was removed at 35°/20 mm., and the residue treated with more carbonyl chloride (10 g., 0·1 mol.) in dioxan. After 8 days, the solution was worked up as in the previous experiments. The crude oil was crystallised from ether (1 vol.) with good cooling to give *anhydro*-O-*carboxymandelic acid*, m. p. 55—57° (Found : C, 60·25; H, 3·6. $C_9H_6O_4$ requres C, 60·6; H, 3·4%).

(e) *Benzo*-1 : 3-*dioxen*-2 : 4-*dione* (*anhydro*-O-*carboxysalicylic acid*). This was prepared by a slight modification of Dupont's method (*loc. cit.*). Dry disodium salicylate (44 g.), suspended in dry toluene (150 c.c.), was treated at 20° with carbonyl chloride (50 g.) in toluene (100 c.c.). After being stirred for 18 hours at 20°, the mixture was filtered, and the insoluble material repeatedly extracted with toluene at 40° until a sample extract gave no precipitate with light petroleum. The combined toluene liquors

were concentrated at 40°/20 mm. to give a white crystalline solid (35·5 g., 89%), m. p. 113—121° (decomp.). A sample of this was crystallised from boiling benzene, and anhydro-*O*-carboxysalicylic acid separated on cooling; it had m. p. *ca.* 118—120° (decomp.), the m. p. being affected by the rate of heating (Found: C, 58·6; H, 3·0. Calc. for $C_8H_4O_4$: C, 58·5; H, 2·5%).

Stability of Anhydrocarboxy-acids.—(a) *To water.* All the derivatives were rapidly decomposed by water with evolution of carbon dioxide. They should therefore be handled and stored in a dry atmosphere.

(b) *On storage.* Purified anhydro-*O*-carboxyglycollic acid was kept for 3 weeks at room temperature protected from moisture by a magnesium perchlorate tube. The loss in weight was 3·9%, corresponding to 10% decomposition with loss of carbon dioxide. Crude material (68% pure) lost about 3·0% by weight under similar storage conditions.

(c) *To heat.* (i) Anhydro-*O*-carboxyglycollic acid. Purified material was heated for 18 hours at 80°. Carbon dioxide was evolved at 60° but the evolution of gas was still slow at 80°. A white solid (polyglycollide) was obtained, m. p. 207—211°. The loss in weight was 37·6% [Calc. for formation of $(O{\cdot}CH_2{\cdot}CO)_n$: 43·2%]. (ii) Anhydro-*O*-carboxylactic acid. Purified material was heated at 100° for 18 hours. There was a loss in weight of 5·4% but the residual oil readily solidified on cooling (m. p. 26·5—27·5°). Analysed by the method of CO_2-loss in water, this was 95% pure, so the compound was but little affected by the heat treatment. (iii) Anhydro-*O*-carboxymandelic acid. This was heated for 16 hours at 120° to give a viscous gum. The loss in weight was 10% [Calc. for $(O{\cdot}CHPh{\cdot}CO)_n$: 24·6%]. (iv) Anhydrocarboxy-*O*-salicylic acid. This was heated at 120° for 2½ hours and then at 170° for 4½ hours. The loss in weight was 26·0% [Calc. for $(C_7H_4O_2)_n$: 26·8%].

Reactions of Anhydrocarboxy-acids.—(a) *With aniline.* The anhydrocarboxy-acid (1 mol.) in dioxan was treated with a solution of aniline (2 mols.) in dioxan, the temperature being kept at 10°. An exothermic reaction occurred. In the case of the anhydrocarboxy-α-substituted acids, carbon dioxide was evolved. When this was complete, the solvent was removed at 40°/15 mm., and the residue dissolved in ether. The ethereal extract was washed successively with dilute sodium hydroxide, dilute hydrochloric acid, and water. The ethereal solution was dried, and the solvent removed. The resulting anilides were: glycollic, m. p. 90—92° (lit., m. p.s 92° and 96°); α-mercaptoacetic, m. p. 107—110° (lit., m. p.s 106° and 111°); lactic, m. p. 56—58° (after crystallisation from *cyclo*hexane) (lit., m. p. 58°); mandelic, m. p. 150—152° (after crystallisation from ethanol) (lit., m. p. 151—152°).

With anhydro-*O*-carboxysalicylic acid, no carbon dioxide was evolved on adding the dioxan solution of aniline, and a solid slowly separated. After 18 hours, the solid was collected: this melted at 126—130° but resolidified and then melted with decomposition at 185—189°. Crystallisation from ethyl acetate gave prisms, m. p. 186—189° (decomp.), but if put in a bath at 140°, the crystals melted and rapidly resolidified. This was apparently the aniline salt of *o*-carboxyphenyl phenylcarbamate. The salt was triturated with water containing sufficient hydrochloric acid to keep the solution just acid to Congo-red. The solid was collected and washed, and the acid filtrate was shown by the Runge test to contain aniline. The solid was crystallised from chloroform to give *o-carboxyphenyl phenylcarbamate*, m. p. 148—150° (decomp.) (Found: C, 65·4; H, 4·3; N, 5·7. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3; N, 5·45%).

(b) *With benzene.* (i) Anhydro-*O*-carboxyglycollic acid. The anhydrocarboxy-compound (5·8 g.) was added slowly to a stirred suspension of aluminium chloride (16 g.) in benzene (60 c.c.), the temperature being kept at 10°. The reaction was exothermic, and a thick gum formed which prevented stirring. After a few minutes, hydrogen chloride began to be evolved, and the gum hardened and broke up so that stirring could be re-started. The mixture was stirred for 2½ hours at 10° and then for 16 hours at room temperature: evolution of hydrogen chloride ceased after the first hour. The mixture was poured into ice-water containing hydrochloric acid, and more benzene added to dissolve the precipitate. The benzene layer was washed with dilute hydrochloric acid, dried and clarified with charcoal. The solvent was removed, leaving phenacyl alcohol (6·5 g., 84·5%), m. p. 84·5—86° (lit., m. p. 86—87°). (ii) Anhydro-*O*-carboxysalicylic acid. A well-stirred suspension of aluminium chloride (58·6 g.) in benzene (350 c.c.) was treated with powdered anhydrocarboxy-acid (32·8 g.) at 20°. The mixture was stirred for 1 hour, then warmed to 80° during ½ hour, and kept at 80° for 2 hours. The product was poured into ice-water containing more than an equivalent of hydrochloric acid to break down the stable complex. The benzene layer was clarified with kieselguhr and washed with aqueous sodium carbonate and with water. The benzene solution was dried, the solvent removed, and the crude *o*-hydroxybenzophenone (28·9 g., 73%) was distilled, b. p. 103°/0·15 mm., m. p. 37—38° (lit., m. p. 39°); oxime, m. p. 143—144° (lit., m. p. 142—143°).

(c) *With acenaphthene.* A suspension of aluminium chloride (50 g.) in carbon disulphide (250 c.c.) was treated with technical 95% acenaphthene (28 g.) followed by anhydro-*O*-carboxyglycollic acid (18·5 g.) at 20°. The viscous gum became stirrable after 1 hour. The mixture was stirred for 16 hours at 20°, refluxed for 4 hours, cooled, and poured into acidified ice-water. The insoluble material was collected and repeatedly extracted with warm carbon disulphide. The combined carbon disulphide liquors were concentrated to yield a yellow solid (11·0 g., 29%), m. p. 133—135°. This was crystallised from benzene and from ethanol to give 5(?)-*α-hydroxyacetylacenaphthene*, m. p. 135—137°, as yellow prisms (Found: C, 79·4; H, 5·2. $C_{14}H_{12}O_2$ requires C, 79·25; H, 5·6%). Treatment with acetic anhydride in pyridine gave 5(?)-*α-acetoxyacetylacenaphthene* as white needles, m. p. 111—112° (Found: C, 75·35; H, 5·5. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

IMPERIAL CHEMICAL INDUSTRIES LIMITED,
RESEARCH LABORATORIES, HEXAGON HOUSE,
MANCHESTER, 9.

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303. *The Kinetics of Exchange Reactions. Part IV. Substituted Phenyl and Benzyl Bromides.*

By (the late) S. Sugden and J. B. Willis.

The exchange of radioactive bromide ion with a number of substituted phenyl and benzyl bromides in ethylene diacetate has been studied. In all cases the non-exponential term in the Arrhenius equation was found to increase with the withdrawal of electrons from the benzene ring, which suggests that the approach of the attacking anions is facilitated by the "thinning" of the π-electron screen round the ring. With increasing electron withdrawal from the ring the activation energy falls in the phenyl series and rises in the benzyl series: it seems that in the former the influence of electron displacement is chiefly on the formation of the new C–Br bond, whereas in the latter it mainly affects the breaking of the initial bond.

As a continuation of earlier work on isotopic exchange reactions of organic bromo-compounds with radioactive bromide ion (Le Roux and Sugden, *J.*, 1939, 1279; Elliott and Sugden, *ibid.*, p. 1836; Le Roux, Lu, Sugden, and Thomson, *J.*, 1945, 586), the reaction

$$RBr + Br^{*-} \rightleftharpoons RBr^{*} + Br^{-}$$

has been investigated for a series of phenyl and benzyl bromides with lithium bromide in ethylene diacetate.

Improvements in technique, together with the availability of radio-bromine of much higher activity, have enabled more accurate results to be obtained than was possible in the earlier work.

The concentration of organic bromide in the reaction mixture was 0·050M. in all cases, and that of lithium bromide 0·030M. Any effect caused by incomplete dissociation of the lithium bromide (cf. Evans and Sugden, *J.*, 1949, 270) is therefore eliminated. No conductivity measurements in ethylene diacetate are at present available, but since there was found to be no measurable variation of rate constant with lithium bromide concentration over the range 0·01—0·1M. it is probable that the degree of dissociation of lithium bromide does not vary over this range.

Experimental.

Materials.—cyclo*Hexylmethyl bromide.* *cyclo*Hexylmethylcarbinol was prepared by the action of paraformaldehyde on the Grignard reagent from *cyclo*hexyl bromide (Adams and Noller, *Org. Synth.*, 1926, **6**, 22). This was converted into the bromide by phosphorus tribromide at 0° (Hiers and Adams, *J. Amer. Chem. Soc.*, 1926, **48**, 2385). The product, dried over freshly ignited potassium carbonate and distilled in *vacuo*, had b. p. 60—62°/10 mm., n_D^{25} 1·4891.

Picryl bromide. The best method of preparation was found to be the nitration of bromobenzene by a modification of the methods of Frankland and Garner (*J. Soc. Chem. Ind.*, 1920, **39**, 257) and of Jackson and Earle (*Amer. Chem. J.*, 1903, **29**, 212). Bromobenzene (25 ml.) was heated at 140° for 17 hours with concentrated sulphuric acid (300 ml.) and fuming nitric acid (*d* 1·51; 100 ml.). The crystals which separated were heated at 140° for a further 12 hours with half of the above quantities of acids, and the mixture then cooled and poured into ice-water. The product, recrystallised twice from alcohol, had m. p. 122—123·5°.

Benzyl bromide. Material of laboratory reagent grade (B.D.H.) was dried (K_2CO_3) and distilled: the fraction of b. p. 196—197° was kept over potassium carbonate and then distilled in *vacuo*. The colourless product had b. p. 55°/2 mm., n_D^{25} 1·5728.

p-*Nitrobenzyl bromide.* A commercial specimen, crystallised twice from 90% aqueous alcohol, had m. p. 99—99·5°.

2 : 4-*Dinitrobenzyl bromide.* *p*-Nitrobenzyl chloride (35 g.) was suspended in concentrated sulphuric acid (155 ml.), and nitric acid (21 ml.) added at <25°. After 30 minutes the mixture was poured on crushed ice, and the 2 : 4-dinitrobenzyl chloride filtered off. This was heated with sodium bromide (35 g.) in 90% aqueous acetone (250 ml.) for 3 hours. The acetone was distilled off, and the residue extracted with water, recrystallised three times from alcohol, and dried in *vacuo*; it had m. p. 46—46·5°.

p-*Cyanobenzyl bromide.* *p*-Tolunitrile was brominated at 200°, the product extracted with hot benzene, and the solvent allowed to evaporate at room temperature. The residue was purified by sublimation in *vacuo* at 110°, recrystallisation from alcohol, and resublimation. The white product had m. p. 114·5°.

p-*Methoxybenzyl bromide.* *p*-Anisaldehyde was reduced to the alcohol by Carothers and Adams's method (*J. Amer. Chem. Soc.*, 1924, **46**, 1675) and treated in benzene with dry hydrogen bromide. The bromide, purified by two distillations in an all-glass apparatus at 0·3—0·4 mm. of nitrogen, was a pale amber-coloured liquid, b. p. 91°/0·3 mm., n_D^{25} 1·5790. Considerable resinification occurred even when a

relatively pure product was distilled. Bromine was determined by silver nitrate (a very rapid reaction) (Found : Br, 39·2. Calc. for C_8H_9OBr : Br, 39·8%). The compound is very unstable (cf. Späth, *Monatsh.*, 1913, **34**, 2000; Baker, *J.*, 1932, 2631). For the present work a stock solution was made in ethylene diacetate through which nitrogen had been bubbled, and the kinetic runs were carried out as soon as possible. No irregularities were noted in the experimental results to indicate decomposition of such solutions.

Ethylene diacetate. Commercial " ethylene glycol diacetate " was distilled in an all-glass apparatus, and the first 20% rejected to eliminate water. This treatment proved adequate, as was shown by tests of the rate of reaction of *p*-cyanobenzyl bromide and lithium bromide at −7·40° in samples of ethylene diacetate treated as shown in Table I. The effect of small amounts of water is in agreement with the view expressed by Hughes and Ingold (*J.*, 1935, 244) that increased solvation should retard the rate of a S_N2 reaction.

TABLE I.

Reaction of p*-cyanobenzyl bromide with lithium bromide at* −7·40°.

Treatment of solvent.	10^4k (l. mole^{-1} sec.$^{-1}$).
Simple distillation	2·28
Redistilled after being dried over anhyd. $CuSO_4$	2·31
Redistilled in *vacuo* after being dried over $Mg(ClO_4)_2$	2·29
0·5% of water added	1·59
0·75% of water added	1·40

The coefficient of expansion by heat of ethylene diacetate, determined by measurements of the density, was 0·00112 per degree over the range 15—100°.

Thermostats.—Ordinary water-filled thermostat baths served for temperatures between 15° and 50°. Temperatures down to −30° were obtained by the use of a wide-mouthed Dewar flask containing alcohol. Cooling was provided by a jacketed tube, filled with solid carbon dioxide and acetone, dipping into the alcohol. A small electric heater controlled in the ordinary way served to keep the temperature constant to within ±0·02°. For temperatures up to 150° a thermostat bath filled with heavy oil was used and was accurate to ±0·05°.

Radio-bromine.—The earlier runs were carried out with lithium bromide prepared by neutron irradiation of ethylene dibromide (Lu and Sugden, *J.*, 1939, 1273). Later, extremely active specimens were produced by the neutron bombardment of sodium bromate or ammonium bromide in the pile at Harwell, and were converted into lithium bromide in this Laboratory.

Counting Equipment.—All-glass β-ray counters of the annular type containing *ca.* 10 ml. of liquid were used. They were constructed in these Laboratories, and supplemented in the later work by several counters purchased from Alltools Ltd. The impulses were amplified and fed to a scaling unit, either a Wynne-Williams scale-of-eight or a Morley-Duke scale-of-thirty-two.

Kinetic Technique.—The technique of Le Roux and Sugden (*loc. cit.*) had to be greatly modified, as it was found to be unsuitable for work using ethylene diacetate as solvent. Radioactive lithium bromide was thoroughly dried by heating it just below its point of fusion, and dissolved in ethylene diacetate to give a solution of twice the concentration required in the reaction mixture; the strength of this solution was determined by a Volhard titration. Equal quantities of the lithium bromide solution and of a 0·100M-stock solution of the aryl bromide in ethylene diacetate were pipetted one into each arm of a Y-shaped reaction vessel, and the arms sealed off. The vessel was placed in the thermostat bath and allowed to warm to thermostat temperature before mixing of the contents. The reaction was terminated by removing the vessel from the thermostat, breaking off the end of one arm, and rapidly pouring the contents into a water–benzene mixture in a separating funnel. For 20 ml. of reaction mixture, 10 ml. of water and 40 ml. of benzene were used. The aqueous layer, containing the lithium bromide, was shaken with a further 40 ml. of benzene. Two further quantities (*ca.* 8 ml. and 5 ml.) of water were shaken successively with the two benzene layers to wash out any residual lithium bromide, and the combined aqueous extracts evaporated to *ca.* 10 ml. A small volume of the original solution of lithium bromide was extracted and made up in the same way for counting. With this technique there is no necessity either for complete washing out of the reaction mixture, or for complete recovery of the lithium bromide, though it was found that the above procedure does give practically 100% recovery. The extracted aqueous solutions were kept for 1½ hours before counting, to allow the attainment of radioactive equilibrium (Le Roux and Sugden, *loc. cit.*). Each solution was counted at least twice, and the rate of decay at some standard time found, so that after titration for bromide ion by the usual Volhard method the activity per unit concentration of bromide could be calculated.

In the reaction

$$\underset{a}{RBr} + \underset{(c-x)}{Br^{*-}} \underset{k}{\overset{k}{\rightleftharpoons}} \underset{x}{RBr^{*}} + \underset{b}{Br^-}$$

it may readily be shown that, since $x \ll a$ and $c \ll b$,

$$k = -\frac{2{\cdot}303}{t(a+b)} \log_{10}\left[1 - \frac{x}{c}\left(1 + \frac{a}{b}\right)\right]$$

The quantity $(c - x)/c$, which is the fraction of the original radio-bromide remaining after time t, is the ratio of the activities per unit concentration of bromide ion in the exchanged and the original solution.

The reactants were measured out in pipettes which had been calibrated to deliver ethylene diacetate, and the concentrations of the solutions at the temperature of reaction were corrected for expansion of the solvent. The main source of error in experiments such as these is in the counting of the radioactive solutions. The probable error in counting of n particles from a radioactive source is $0{\cdot}67n^{\frac{1}{2}}$, so that the probable error in counting 10,000 particles, which was about the number counted for any one solution, is less than 0·7%.

Tests for Hydrolysis of Organic Bromides.—Known volumes of the stock solutions of the aryl bromides were extracted with benzene–water as in an actual run, and the aqueous extracts titrated for bromide. Only *p*-methoxybenzyl bromide showed any detectable hydrolysis, and as this amounted at the most to 0·5% no correction was applied to the experimental figures.

Test of the Order of the Reaction.—It is well established that halide exchange reactions are bimolecular in media of low ionising power, and Le Roux and Sugden (*loc. cit.*) showed that the exchanges of several aliphatic bromides with bromide ion have second-order kinetics in acetone, 90% aqueous acetone, and ethylene diacetate. For this reason it was considered sufficient to test the order of reaction for one of the compounds used. For this purpose *p*-nitrobenzyl bromide was studied, at −6·60°. The concentration of organic bromide was varied from 0·02 to 0·10M., and the lithium bromide from 0·01 to 0·10M., but the rate constant, calculated for a second-order reaction, remained constant within experimental error.

Results.

Table II summarises the average rate constants for each substance. The concentration of aryl bromide in every case was 0·050M. and that of lithium bromide was 0·030M.

Table II.

Compound.	Temp.	No. of results.	10^4k (l. mole^{-1} sec.$^{-1}$).	Compound.	Temp.	No. of results.	10^4k (l. mole^{-1} sec.$^{-1}$).
*cyclo*Hexylmethyl bromide	89·73°	8	1·23	*p*-Nitrobenzyl bromide	− 5·10°	6	4·57
	99·61	9	2·67		0·00	8	7·56
	111·40	8	6·13		5·58	8	13·7
	122·20	12	11·9		11·39	5	24·5
					15·18	7	33·7
Picryl bromide	− 5·30	9	1·99		20·00	9	54·1
	0·00	12	3·92				
	10·19	9	13·1	2 : 4-Dinitrobenzyl bromide	−27·29	5	3·10
	21·62	9	45·3		−19·94	3	8·16
					− 6·60	6	42·0
Benzyl bromide	5·58	8	1·21				
	16·86	6	3·38	*p*-Cyanobenzyl bromide	− 7·40	9	2·29
	24·91	13	7·89		4·78	9	9·47
	34·90	9	16·8		15·14	11	27·1
	44·88	11	36·4		25·01$_5$	9	75·9
p-Methoxybenzyl bromide	− 5·30	6	3·14				
	4·88	8	8·33				
	14·80	8	20·0				
	25·00	9	45·2				

Table III.

Bromide.	10^4k_{25} (l. mole^{-1} sec.$^{-1}$).	A.	E' (kcals.).	σ (A.).
*cyclo*Hexylmethyl	0·00284	6·81 ± 0·08	19·88 ± 0·14	0·18
2 : 4-Dinitrophenyl *	0·00287	6·42 ± 0·13	19·34 ± 0·23	0·09
Picryl	64·8	9·73 ± 0·09	17·93 ± 0·12	3·93
Benzyl	7·40	6·62 ± 0·07	14·97 ± 0·10	0·11
p-Nitrobenzyl	83·2	7·77 ± 0·06	15·11 ± 0·08	0·40
2 : 4-Dinitrobenzyl	1130	9·66 ± 0·07	16·14 ± 0·08	3·61
p-Cyanobenzyl	73·8	8·79 ± 0·04	16·57 ± 0·05	1·77
p-Methoxybenzyl	45·6	6·45 ± 0·06	13·66 ± 0·08	0·09

* Le Roux, Lu, Sugden, and Thomson, *loc. cit.*

All the reactions followed the Arrhenius law, and Table III gives the parameters of the modified Arrhenius equation

$$\log_{10}(k/T^{\frac{1}{2}}) = A - 1000E'/4{\cdot}57T \quad (E' \text{ is in kcals.})$$

The Arrhenius activation energy is approximately 0·3 kcal./mole greater than E'. Table III also gives the rate constant calculated for an arbitrary temperature (25°), and the effective collision diameter σ, calculated as described by Le Roux and Sugden (*loc. cit.*). The probable

errors were obtained during the calculation of A and E' by a " least-squares " treatment of all the velocity constants for the compound. Too much significance should not be attached to these probable errors, as the statistical method fails to allow for any systematic errors.

Discussion.

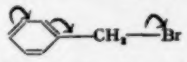
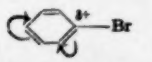
*cyclo*Hexylmethyl bromide is non-aromatic and gives almost the same values as were found earlier for *iso*propyl bromide in ethylene diacetate ($A = 6{\cdot}71 \pm 0{\cdot}09$; $E' = 19{\cdot}75 \pm 0{\cdot}15$ kcals.; Le Roux, Lu, Sugden, and Thomson, *loc. cit.*). When the ring becomes aromatic in benzyl bromide there is a fall in E' of nearly 5 kcals., while A remains almost unchanged.

Bromobenzene and *p*-bromonitrobenzene were found (*loc. cit.*) not to undergo exchange at an appreciable rate at temperatures up to 200°, but 1-bromo-2 : 4-dinitrobenzene gave a measurable rate. We have now added picryl bromide to this series. The most striking effect of the accumulation of nitro-groups is the large increase of A, but there is also a small drop in the activation energy.

In the benzyl series, too, the introduction of electron-withdrawing groups (*p*-nitro, 2 : 4-dinitro, *p*-cyano) produces a large increase in A. Conversely, the *p*-methoxy-group, which by its $+T$ effect tends to release electrons into the ring, decreases A. In this series, however, the accumulation of electron-withdrawing groups *raises* the activation energy.

The change of A on the introduction of substituents may be caused by electrostatic shielding of the carbon atoms of the benzene ring by the distribution of π-electrons in layers above and below the ring (cf. Catchpole, Hughes, and Ingold, *J.*, 1948, 4). These will hinder the approach of anions attaching the ring carbon atoms or those on short side-chains, as in benzyl compounds. Substituents such as nitro- or cyano-groups, which withdraw electrons from the ring, will diminish this effect and increase A, whilst electron-repelling groups will have the reverse effect.

The effect of substituents on the distribution of electrons in the ring may be considered in relation to two processes. The first is associated with the stretching of the original C–Br bond, and in the case of benzyl bromide can be formulated as in (*a*). This change will clearly be facilitated by substituents in the ring with a $+T$ effect and opposed by those with a $-T$ effect. The second process is the development of a positive charge on the carbon atom at which substitution occurs, which will attract the attacking anion. This charge cannot conjugate with the ring in benzyl compounds because of the single bond in the side-chain, but in the phenyl series such conjugation is possible as in (*b*). An incipient positive charge is produced at the carbon atom being attacked, and attracts the attacking anion. The effect of substituents will be the reverse of that expected for (*a*).

(*a*)  (*b*) 

In the benzyl series the significant process appears to be (*a*), since (*b*) is prevented by the single bond between the ring and the carbon atom of the side-chain. In agreement with this view *p*-nitro- and *p*-cyano-groups raise the activation energy, whilst a *p*-methoxy-group lowers it. Saturation of the ring, as in *cyclo*hexylmethyl bromide, prevents conjugation and raises the activation energy.

The alternative process (*b*) appears to be the more important for the phenyl derivatives. This would be expected to be so, since conjugation of the ring electrons will hinder the transfer of one of them to the bromine atom to expel it as an anion. In this series it is found experimentally that the nitro-group, which withdraws electrons from the ring and would facilitate process (*b*), lowers the activation energy.

We are very grateful to Professor C. K. Ingold for valuable discussion. The work was carried out in 1946—1948 during the tenure by one of us (J. B. W.) of a Senior Studentship awarded by the Council for Scientific and Industrial Research, Australia. Professor Sugden wrote a rough draft of the paper early in 1949, and after his death in October 1950 it was revised and completed by the junior author (present address : C.S.I.R.O., Division of Industrial Chemistry, Melbourne, Australia).

University College, London, W.C.1. [*Received, February 7th*, 1951.]

304. *Photochemical Reactions in Sunlight. Part XVI.* (a) *Photoreduction of Phenylglyoxylic Acid.* (b) *Photo-reactions between Aldehydes and* o-*Quinones.* (c) *Reactions between* o-*Quinones and Ethylenes in the Dark and in the Light.*

By Alexander Schönberg, Nazih Latif, Radwan Moubasher, and Aly Sina.

s-Dihydroxydiphenylsuccinic acid was obtained by the photo-reduction of phenylglyoxylic acid.

Tetrachloro- and tetrabromo-*o*-benzoquinone and 3 : 4-dichloro-β-naphthaquinone were allowed to react in light with aldehydes (see scheme A).

Tetrabromo-*o*-benzoquinone and 3 : 4-dichloro-β-naphthaquinone react with stilbene in the dark in hot benzene solutions and in cold solutions in sunlight (see scheme B). Tetrachloro-*o*-benzoquinone reacts in light in a similar way with styrene, 1-2′-naphthyl-2-phenylethylene, and 3-phenyl*iso*coumarin.

Phenanthraquinone reacts with xanthotoxin (VIII), khellinone (X*a*), and visnaginone (X*b*) in sunlight, giving the photo-adducts (IX), (XI*a*), and (XI*b*), respectively.

The action of light on 2-phenyl-α-naphthaquinone is discussed.

Photochemical Reduction of Phenylglyoxylic Acid.—Very little seems to be known about the *s*-diaryldihydroxysuccinic acids. *s*-Dihydroxydiphenylsuccinic acid was hitherto unknown; attempts to synthesise it having failed (Steinkopf und Wolfram, *Annalen*, 1923, **430**, 122; Burton, *Ber.*, 1883, **16**, 2232), but by photochemical reduction of phenylglyoxylic acid in the presence of *iso*propyl alcohol, *i.e.*, in the absence of acids, alkalis, salts, etc., we obtained this acid in good yield. When heated it decomposes to give *iso*hydrobenzoin.

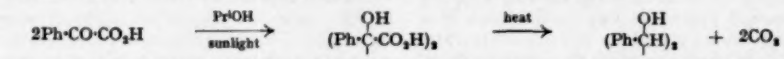
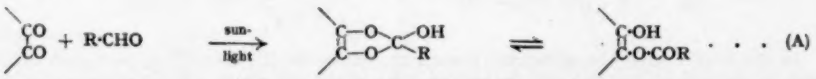
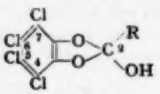


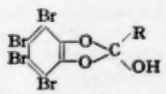
Photo-action of Aldehydes on Derivatives of o-*Benzoquinone and* β-*Naphthaquinone.*—It has been shown (Schönberg and Moubasher, *J.*, 1939, 1430; Mustafa, *J.*, 1949, S 83) that the photo-addition products of phenanthraquinones with aldehydes are to be regarded as derivatives of methylene ethers of 9 : 10-dihydroxyphenanthrene, exhibiting ring-chain tautomerism as follows:



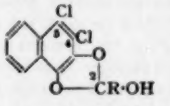
Similar products from *o*-benzoquinone and β-naphthaquinone have not yet been described. In view of the instability of these two quinones, we have used their halogenated derivatives and obtained the products (I*a*)—(III), analogous to the foregoing photo-products. In most cases the



(I*a*; R = Me.)
(I*b*; R = Ph.)
(I*c*; R = *p*-Me·C$_6$H$_4$·)
(I*d*; R = *p*-MeO·C$_6$H$_4$·)
(I*e*; R = CH:CHPh.)



(II*a*); R = *p*-Me·C$_6$H$_4$·)
(II*b*; R = *p*-MeO·C$_6$H$_4$·)



(III; R = *p*-MeO·C$_6$H$_4$·)

photo-products separated in good yield as almost pure crystals during irradiation. The ferric chloride reaction shown by the photo-addition products and the solubility in alkali (see Table I) are in agreement with the open-chain form (see scheme A).

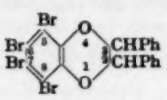
As it is established that methylene ethers of *o*-dihydroxy-compounds may be formed by photo-addition of aldehydes to phenanthraquinones [*e.g.*, chrysoquinone (Schönberg and Moubasher; Mustafa (*locc. cit.*); acenaphthenequinone (Sircar and Sen, *J. Indian Chem. Soc.*,

1931, **8**, 605)] as well as to derivatives of *o*-benzoquinone and β-naphthaquinone, reaction (A) can now be regarded as typical for *o*-quinones.

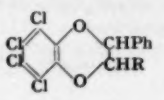
Dark and Photo-reactions between o-Quinones and Ethylenes.—Recently Schönberg and Latif (*J. Amer. Chem. Soc.*, 1950, **72**, 4828) stated that tetrachloro-*o*-benzoquinone differs from all other quinones and similar compounds previously investigated in that it reacts with ethylenes, not only in the light, but also in the dark:

(B)

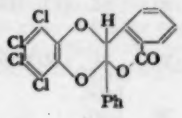
We have now found similar behaviour in the dark by tetrabromo-*o*-benzoquinone and 3 : 4-dichloro-β-naphthaquinone towards stilbene, leading to (IV) and (VII), respectively. Also, the reactions recorded in Table II were carried out in sunlight. They proceed according to scheme (B). In agreement with the proposed formulæ for the products are the fact that they are colourless, or almost so, and the results of their pyrolysis.



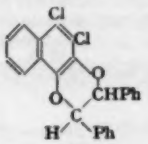
(IV.)



(Va; R = H.)
(Vb; R = β-Naphthyl.)



(VI.)



(VII.)

Photo-action between Phenanthraquinone and Xanthotoxin and Related Compounds.—Xanthotoxin (VIII), a major constituent of the fruits of *Ammi majus* (Schönberg and Sina, *Nature*, 1948, **161**, 481; *J. Amer. Chem. Soc.*, 1950, **72**, 4862), contains two double bonds, one in the five-, and the other in the six-membered heterocyclic ring, both of which might react with phenanthraquinone. However, in our experiment only one molecule of phenanthraquinone was added, with the formation of (IX). This formula is based on analogy; coumarin does not

TABLE I.

(Reaction A).

(For systematic names, see Table III.)

o-Benzoquinone and wt. (g.).	Aldehyde, and wt. (g.).	C_6H_6, c.c.	Time of irradiation, days.	M. p. (and colour with $FeCl_3$[1]) of addition product.*	Formula.	Analysis of addition product. Found, %. C.	H.	Cl(Br).	Reqd., %. C.	H.	Cl(Br).
Tetrachloro- (0·4)	Acetaldehyde (0·3)	20	3 (March)	(Ia),[2] 128—130°	$C_8H_4O_2Cl_4$	33·8	1·3	48·1	33·1	1·3	48·9
Tetrachloro- (1·0)	Benzaldehyde (0·5)	25	10 (Nov.)	(Ib), 174°,[3] yellow	$C_{13}H_8O_2Cl_4$	44·5	2·0	—	44·3	1·7	—
Tetrachloro- (0·8)	*p*-Tolualdehyde (0·4)	30	10 (Dec.)	(Ic), 201°	$C_{14}H_8O_2Cl_4$	46·3	2·3	39·0	45·9	2·1	38·7
Tetrachloro- (1·0)	Anisaldehyde (0·5)	25	5 (Dec.)	(Id), 208°,[4,5] yellow	$C_{14}H_8O_4Cl_4$	43·9	2·3	37·4	43·9	2·0	37·1
Tetrachloro- (0·8)	Cinnamaldehyde (0·4)	40	7 (Dec.)	(Ie),[5] 187°, yellow	$C_{15}H_8O_2Cl_4$	47·5	1·8	37·4	47·6	2·1	37·5
Tetrabromo- (0·8)	*p*-Tolualdehyde (0·4)	20	20 (Feb.)	(IIa), 221°	$C_{14}H_8O_2Br_4$	30·9	1·4	(58·3)	30·8	1·4	(58·8)
Tetrabromo- (2)	Anisaldehyde (1·2)	30	4 (Jan.)	(IIb), 246°	$C_{14}H_8O_4Br_4$	30·2	1·5	(57·0)	30·0	1·4	(57·1)
3 : 4-Dichloro-β-naphthaquinone (0·7)	Anisaldehyde (1·0)	25	2 (May)	(III), 207°[6]	$C_{18}H_{12}O_4Cl_2$	60·0	3·5	19·3	59·5	3·3	19·5

* All eight products were colourless (or very nearly so). All were ultimately crystallised from benzene, except IIa (from xylene).

[1] The reaction was carried out by adding to a cold alcoholic solution of the substance an aqueous solution of ferric chloride. [2] The benzene was evaporated to very small bulk; addition of light petroleum (b. p. 30—50°) then precipitated an oil. The liquid was decanted and to the residue a few c.c. of benzene were added; when left to concentrate slowly, the liquid deposited crystals, which were washed with benzene. [3] Yield, 70%. [4] Yield, almost quantitative. [5] The product dissolved when treated with 6% alkali. [6] Deposited crystals first washed with light petroleum (b. p. 40—60°).

TABLE II

(Reaction B).

(For names of products, see Table III.)

Quinone, and wt. (g.).*	Ethylene deriv., and wt. (g.).	C_6H_6, c.c.	Time of irradiation, days.	Product and m.p.[3]	Formula.	Analysis of addition product. Found, %. C.	H.	Cl(Br).	Reqd., %. C.	H.	Cl(Br).
A (1·2)	Stilbene (0·5)	30	20 (Jan.)	(IV), 215° (decomp.)	$C_{20}H_{12}O_2Br_4$	40·0	1·7	(53·7)	39·7	1·9	52·9
A (1·2)	Stilbene (0·5)	30	Dark expt.[1]	,, ,,	—	—	—	—	—	—	—
B (0·8)	Styrene (0·4)	30	12 (Dec.)	(Va), 79°	$C_{14}H_8O_2Cl_4$	47·9	1·8	—	47·9	2·2	—
B (0·4)	1-2′-Naphthyl-2-phenylethylene (0·3)	20	10 (Dec.)	(Vb), 180°	$C_{24}H_{14}O_2Cl_4$	61·0	3·3	28·9	60·5	2·9	29·8
B (0·3)	3-Phenyl*iso*coumarin (0·2)	20	15 (Jan.)	(VI), 159°	$C_{21}H_{10}O_4Cl_4$	53·8	2·1	30·1	53·7	2·1	30·3
C (0·9)	Silbene (0·7)	25	21 (May–June)	(VII), 165°	$C_{34}H_{16}O_2Cl_2$	70·6	3·9	—	70·7	3·9	—
C (0·8)	Stilbene (0·6)	30	Dark expt.[2]	,, ,,	—	—	—	—	—	—	—
D (0·42)	Xanthotoxin (VIII) (0·43)	30	3 (Feb.)	(IX), 230° (decomp.)	$C_{24}H_{16}O_6$	73·3	3·9	—	73·6	3·8	—
D (0·8)	Khellinone (X*a*) (0·95)	40	3 (May)	(XI*a*), 231° (decomp.; red-brown melt) [4]	$C_{26}H_{20}O_7$	70·4	4·5	—	70·3	4·5	—
D (0·8)	Visnaginone (X*b*)	40	3 (May)	(XI*b*), 200—220° (decomp.) [4, 5]	$C_{22}H_{18}O_6$	72·5	4·7	—	72·5	4·4	—
D (0·42)	Coumarin (0·29)	25	14 (March)	Nil	—	—	—	—	—	—	—

* A = Tetrabromo-*o*-benzoquinone. B = Tetrachloro-*o*-benzoquinone. C = 3 : 4-Dichloro-β-naphthaquinone. D = Phenanthraquinone.

[1] 10 Hours' refluxing. [2] 14 Hours' refluxing. [3] For methods of working up products, see later footnotes correspondingly numbered. All the products were colourless or nearly so, except that (IX) was pale yellow. The products of the two "dark" experiments were identical (mixed m. p.) with those from the corresponding irradiation experiments. [4] $FeCl_3$ reaction: red-brown. The reaction was carried out as noted under Table I (footnote 1). [5] The crystals gradually became reddish.

Working-up of Products.—In the following, D denotes the deposit formed during illumination, and R the residue obtained from the irradiated mixture after filtration and evaporation of solvent.

(IV). R was treated with a few c.c. of acetone; the crystals which separated were recrystallised from the same solvent.

(IV) (Dark expt.). As above, but R was crystallised from glacial acetic acid.

(V*a*). R was extracted with hot light petroleum (b. p. 60—80°). The extract was filtered and evaporated, and the oily residue cooled in ice; crystallisation occurred on scratching, and treatment with methyl alcohol afforded a pale yellow solid. This was dissolved in the minimum amount of hot benzene and left overnight. After the addition of a few c.c. of absolute alcohol, crystals separated.

(V*b*). R was treated with cold, absolute alcohol; the pale yellowish-brown solid which separated was dissolved in a very little hot benzene, the solution filtered, and methyl alcohol added till turbidity occurred. On slow cooling, a pale yellow solid separated and was recrystallised from acetone–absolute alcohol.

(VI). R was crystallised from acetone–methyl alcohol.

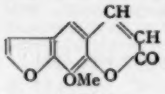
(VII). R was extracted with absolute alcohol, and then dissolved in a very little hot benzene. Light petroleum (b. p. 30—50°) was added dropwise till turbidity occurred, followed by a few c.c. of ether. Slow evaporation at room temperature afforded crystals, which were recrystallised from acetone with cooling to 0°.

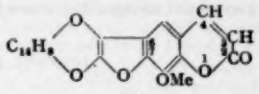
(IX). The crystalline D was washed repeatedly with alcohol; it was difficultly soluble in hot alcohol, benzene, and light petroleum (b. p. 60—90°) and soluble in hot nitrobenzene.

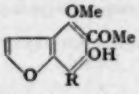
(XI*a*). D was difficultly soluble in hot alcohol and light petroleum (b. p. 60—90°), and soluble in hot benzene, from which it was recrystallised.

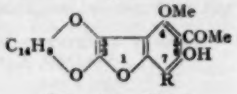
(XI*b*). D was recrystallised from hot benzene; it was difficultly soluble in alcohol.

react photochemically with phenanthraquinone, whereas the benzofuran derivatives, khellinone (X*a*), visnaginone (X*b*), and 2 : 3-diphenylbenzofuran (Mustafa and Islam, *J.*, 1949, S 81), do so. For the photo-products obtained from phenanthraquinone and (X*a*) and (X*b*), we suggest formulæ (XI*a*) and (XI*b*), respectively; (IX), (XI*a*), and (XI*b*) when heated give their generators. The photo-behaviour of xanthotoxin is interesting in connection with its use in the light therapy of leukodermia (Fahmy and Abu-Shady, *J. Pharm. Pharmacol.*, 1947, **20**, 281; 1948, **21**, 499; El-Mofty, *J. Roy. Egypt. Med. Assoc.*, 1948, **31**, 1108).


(VIII.)


(IX.)


(X*a*; R = OMe.)
(X*b*; R = H.)


(XI*a*; R = OMe.)
(XI*b*; R = H.)

Action of Light on 2-*phenyl*-1 : 4-*naphthaquinone*.—When benzene solutions of this quinone are exposed to sunlight, a polymer is obtained in almost colourless crystals, which when heated regenerate the monomeric quinone (Breuer and Zincke, *Ber.*, 1878, **11**, 1403; Rügheimer and Hankel, *Ber.*, 1896, **29**, 2176). α-Naphthaquinone gives a similar photo-dimer for which the structure (XII*a*) has been advanced (Schönberg *et al.*, *J.*, 1948, 2126), so we assign the analogous structure (XII*b*) to the phenyl derivative. Neither quinone undergoes polymerisation readily in the solid state.

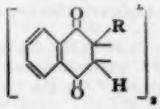

(XII*a*; R = H.)
(XII*b*; R = Ph.)

TABLE III.

Formal names of products given in Tables I *and* II.

Number.	Name.
I*a*	4 : 5 : 6 : 7-Tetrachloro-2-hydroxy-2-methylbenzodioxole.
I*b*	4 : 5 : 6 : 7-Tetrachloro-2-hydroxy-2-phenylbenzodioxole.
I*c*	4 : 5 : 6 : 7-Tetrachloro-2-hydroxy-2-*p*-tolylbenzodioxole.
I*d*	4 : 5 : 6 : 7-Tetrachloro-2-hydroxy-2-*p*-methoxyphenylbenzodioxole.
I*e*	4 : 5 : 6 : 7-Tetrachloro-2-hydroxy-2-styrylbenzodioxole.
II*a*	4 : 5 : 6 : 7-Tetrabromo-2-hydroxy-2-*p*-tolylbenzodioxole.
II*b*	4 : 5 : 6 : 7-Tetrabromo-2-hydroxy-2-*p*-methoxyphenylbenzodioxole.
III	4 : 5-Dichloro-2-hydroxy-2-*p*-methoxyphenyl-α-naphthodioxole.
IV	5 : 6 : 7 : 8-Tetrabromo-2 : 3-diphenylbenzodioxen.
V*a*	5 : 6 : 7 : 8-Tetrachloro-2-phenylbenzodioxen.
V*b*	5 : 6 : 7 : 8-Tetrachloro-3-2′-naphthyl-2-phenylbenzodioxen.
VI	5 : 6 : 7 : 8-Tetrachloro-2-phenyl*iso*coumarino(3′ : 4′-2 : 3)benzodioxen.
VII	3′ : 4′-Dichloro-5 : 6-diphenylnaphtho(1′ : 2′-2 : 3)dioxen.
IX	4′ : 5′-Phenanthrylenedioxyfurano(3′ : 2′-6 : 7)*iso*coumarin.
XI*a*	5-Acetyl-4 : 7-dimethoxy-2 : 3-phenanthrylenedioxybenzofuran.
XI*b*	5-Acetyl-4-methoxy-2 : 3-phenanthrylenedioxybenzofuran.

EXPERIMENTAL.

Pure benzene dried over sodium was used. The photochemical reactions were carried out in Pyrex-glass tubes sealed under carbon dioxide.

Action of iso*Propyl Alcohol on Phenylglyoxylic Acid.*—Phenylglyoxylic acid (2 g.) and *iso*propyl alcohol (20 g.) were left in sunlight for 4 weeks (May–June). The acid dissolved gradually to give a colourless solution. The illuminated solution was concentrated in a vacuum; the *s-dihydroxydiphenylsuccinic acid* was recrystallised first from benzene–light petroleum (b. p. 60—80°) and then from ligroin, forming colourless needles (1·2 g.), m. p. 155°, soluble in cold sodium hydroxide solution; the alcoholic solution reacted with aqueous sodium hydrogen carbonate solution with evolution of gas (Found: C, 63·2; H, 4·3; active H, 1·1. $C_{14}H_{14}O_6$ requires C, 63·6; H, 4·6; active H, 1·2%).

Pyrolysis of photo-product. The photo-product was heated at 160° (bath-temp.) for 15 minutes under reduced pressure; an oily residue was obtained which solidified after 24 hours; the colourless crystals proved to be *iso*hydrobenzoin (m. p. and mixed m. p.).

Thermal Decomposition.—(a) *Of* (VII). This product was heated in a boiling ethyl phthalate bath under reduced pressure (oil-pump) for 15 minutes. The reaction vessel was left to cool in a vacuum, and the crystals collecting on the upper parts were recrystallised from methyl alcohol and proved to be stilbene (m. p. and mixed m. p.).

(b) *Of* (IX). The heating was carried out for 15 minutes, in an ethyl cinnamate bath; a mixture of brown and light-coloured crystals was formed on the walls of the tube. This was treated with 10% sodium hydroxide solution and filtered: filtrate (*f*), precipitate (*p*); (*p*) was purified by dissolving it in concentrated sulphuric acid and pouring the solution into water; the precipitate formed was washed with water and recrystallised from alcohol as orange crystals of phenanthraquinone (m. p. and mixed m. p.); (*f*) was acidified with hydrochloric acid, and the precipitate formed was washed with water and then separated from methyl alcohol as colourless crystals of xanthotoxin (m. p. and mixed m. p.; yellow colour with concentrated sulphuric acid).

(c) *Of* (XI*a*) *and* (XI*b*). Thermal decomposition and isolation of the products (phenanthraquinone and khellinone or visnaginone, respectively) were carried out as described under (b).

FACULTY OF SCIENCE, FOUAD I UNIVERSITY,
ABBASSIA, CAIRO, EGYPT.

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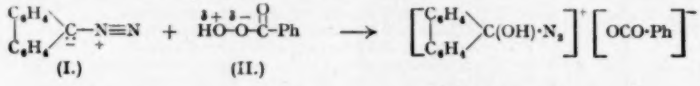
NOTES.

305. *Experiments with Diazomethane and its Derivatives. Part XVI. Action of Diazomethanes on Perbenzoic Acid and Benzoquinone Derivatives.*

By ALEXANDER SCHÖNBERG, WILLIAM IBRAHIM AWAD, and NAZIH LATIF.

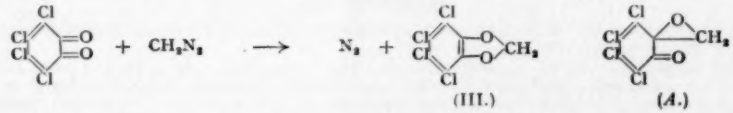
VERY little seems to be known about the action of peracids on diazohydrocarbons. When a benzene solution containing 9-diazofluorene and perbenzoic acid is warmed, nitrogen is evolved and benzoic acid and fluorenone are formed. On the basis of a positively polarised hydroxyl group in peracids (cf. II) (Swern, *Chem. Reviews*, 1949, **45**, 1; *J. Amer. Chem. Soc.*, 1947, **69**, 1692; Derbyshire and Waters, *Nature*, 1950, **165**, 401) and the electronic formula (I) for 9-diazofluorene (cf. Eistert, "Newer Methods of Preparative Organic Chemistry," Interscience Publ., 1948, p. 514) the reaction may be formulated as follows:



(I.) (II.)

9-Diazofluorene (the preparation of which we have improved) is a particularly suitable substance for investigation of the action of peracids, because fluorenone is markedly stable to peracids.

Continuing our work on *o*-quinones, we have investigated the action of diazomethane and diphenyldiazomethane on tetrachloro- and tetrabromo-*o*-benzoquinone, which are stable substances in contrast to *o*-benzoquinone itself. The reaction proceeded in all cases as illustrated below; for the mechanism of the reaction see Schönberg and Awad, *J.*, 1950, 72.



(III.) (*A*.)

In accordance with the proposed constitution, the reaction products are colourless or almost so, and they are rather stable towards acids. This excludes the formation of an ethylene oxide ring (as *A*); it is stated that in the case of phenanthraquinone and diazomethane two substances are formed, namely, the analogues of (III) and (*A*) respectively (Arndt, Amende, and Ender, *Monatsh.*, 1932, **59**, 210; Biltz and Paetzold, *Annalen*, 1923, **433**, 71, 81).

Experimental.—*9-Diazofluorene.* Fluorenone hydrazone (4 g.), mercuric oxide (7 g.), and anhydrous sodium sulphate (2 g.) were ground together for a few minutes, then transferred to a dry, glass-stoppered bottle, and dry ether (50 c.c.) was added. About ½ c.c. of a freshly prepared, concentrated solution of potassium hydroxide in ethyl alcohol was added, the whole shaken for five minutes by hand and then for

30 minutes on the shaker. The reaction started at once, as shown by a dark deposit formed during the hand-shaking. The solution was filtered, the residue was washed with ether, and the washings were combined with the main ethereal solution; this was then concentrated under reduced pressure, red crystals being obtained, m. p. 94—95° (yield, almost quantitative) (cf. Vogel, "Practical Organic Chemistry").

Action of perbenzoic acid on 9-diazofluorene. 9-Diazofluorene (0·5 g.) was dissolved in benzene (12 c.c.), warmed at 45°, and an ice-cold benzene solution (12 c.c.) of the peracid (0·6 gm.) added gradually (benzene, dried over sodium). Evolution of nitrogen occurred and at the end (about 20 minutes) the solution became yellowish-orange in colour. It was evaporated to dryness, the residue treated at once with sodium carbonate solution, and the mixture extracted with benzene. The aqueous layer was treated with dilute hydrochloric acid; a solid was precipitated (0·1 g.), which was crystallised from hot water and proved to be benzoic acid by m. p. and mixed m. p. determinations.

The benzene layer was dried (Na_2SO_4), the benzene driven off *in vacuo*, and the residue left *in vacuo* for 48 hours. The solid residue (0·3 g.) was recrystallised several times from dilute methyl alcohol, and the yellow crystals were proved by m. p. and mixed m. p. determinations to be fluorenone (0·15 g.).

Action of perbenzoic acid on fluorenone. This experiment was carried out with fluorenone (1·8 g.) as described for 9-diazofluorene. Fluorenone (1·1 g.) was recovered (m. p. and mixed m. p.).

3 : 4 : 5 : 6-*Tetrachloro*-1 : 2-*methylenedioxybenzene* (III). Tetrachloro-*o*-benzoquinone (Jackson and MacLaurin, *Amer. Chem. J.*, 1907, **37**, 7) (0·5 g.) in ether was allowed to react in the cold with diazomethane (from nitrosomethylurea; Arndt, *Org. Synth.*, 1935, **15**, 3). A vigorous evolution of gas was observed. After 90 minutes the ether was driven off and the residue crystallised from methyl alcohol as crystals (>80%), m. p. *ca.* 171° (Found: C, 32·3; H, 1·0. Calc. for $C_7H_2O_2Cl_4$: C, 32·3; H, 0·8%). The product was recovered unchanged when heated under reflux in dioxan (5·5 c.c.) and hydrochloric acid (*d ca.* 1·18; 1 c.c.) for 30 minutes.

3 : 4 : 5 : 6-*Tetrabromo*-1 : 2-*methylenedioxybenzene*. This substance (>80% yield) was prepared as above, from tetrabromo-*o*-quinone (Zincke, *Ber.*, 1887, **20**, 1777). It had m. p. 203° (from acetone) (Found: C, 19·7; H, 0·5; Br, 73·0. Calc. for $C_7H_2O_2Br_4$: C, 19·2; H, 0·4; Br, 73·5%).

3 : 4 : 5 : 6-*Tetrachloro*-1 : 2-(*diphenylmethylenedioxy*)*benzene*. To tetrachloro-*o*-benzoquinone (0·5 g.) in benzene was added a small excess of diphenyldiazomethane at room temperature. After 24 hours the benzene was evaporated and the residue treated with a few c.c. of methyl alcohol. A crystalline product was formed which was recrystallised from alcohol as crystals (>80%), m. p. 141° (Found: C, 55·8; H, 2·5; Cl, 34·7. Calc. for $C_{19}H_{10}O_2Cl_4$: C, 55·4; H, 2·4; Cl, 34·4%). The product was unchanged when treated with hydrochloric acid as described above.

FOUAD I UNIVERSITY, ABBASSIA, CAIRO, EGYPT. [*Received, November 10th*, 1950.]

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306. *The Reaction of Diazomethane with Stilbœstrol in the Presence of Propanol.*

By AHMED MUSTAFA.

SCHÖNBERG AND MUSTAFA (*J.*, 1946, 746) reported that stilbœstrol and diazomethane in *n*-propanol–ether gave stilbœstrol di-*n*-propyl ether, but Gerber and Curtin (*J. Amer. Chem. Soc.*, 1949, **71**, 1499) obtained the mono- and the di-methyl ether only. These are indeed, by far, the main products. Schönberg and I would like to state that, in our paper, the use of the words "recrystallisation" and "crystallised" in connection with the isolation of stilbœstrol di-*n*-propyl ether are to be replaced by "fractional crystallisation" and "fractionally crystallised" respectively.

The pure di-*n*-propyl ether is obtained (see below) in quantities enough for microanalysis, but this gives no indication of how much is actually formed. Gerber and Curtin (*loc. cit.*) also identified only 90% of their reaction products.

Experimental.—Stilbœstrol (0·5 g.) (B.D.H.) was dissolved in a mixture of ether (20 c.c.) and *n*-propyl alcohol (freshly distilled) (20 c.c.); to this cold solution, an ethereal solution of diazomethane (prepared from 10 g. of nitrosomethylurea and distilled) was added. The reaction mixture was kept for 48 hours in ice–salt, whereafter further ethereal diazomethane solution (from 10 g. of nitrosomethylurea) was added and the reaction mixture was further kept in the cooling mixture for 24 hours. The ether–alcohol mixture was evaporated under reduced pressure (water-pump) and the solid residue redissolved in cold ether and washed twice with aqueous potassium hydroxide (25%). The ether was then thoroughly washed with water and dried (Na_2SO_4). The ether was then driven off and the solid residue washed several times with cold light petroleum (b. p. 40—60°). The insoluble residue melts at 120—122°. The petroleum extract was further concentrated and then, on cooling, was filtered from the separated crystals (m. p. 120—122°) and the mother-liquor was allowed to evaporate slowly, giving a crystalline residue, m. p. 80—110°. This crystalline residue was then washed several times with cold light petroleum (b. p. 40—60°) and the insoluble part (m. p. 120°) was removed. The last light petroleum extract was concentrated, whereupon crystals separated (m. p. 90—95°) which were further thrice

recrystallised from light petroleum (b. p. 40—60°), giving a small amount of colourless uniform crystals, m. p. 93—96°, enough for one micro-analysis (Found : C, 81·4; H, 9·2. Calc. for $C_{34}H_{32}O_2$: C, 81·8; H, 9·1%). A mixed m. p. with an authentic specimen gave no depression.

The analysis have been done by Dr. Weiler and Dr. Strauss, Oxford, and three concordant analysis of material obtained from three different experiments were obtained.

FOUAD I UNIVERSITY, ABBASSIA,
CAIRO, EGYPT.

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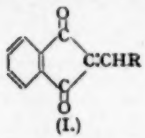
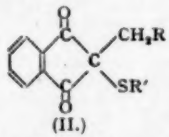
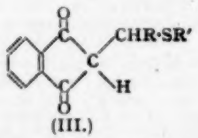
307. *The Addition of Thiols to 2-Arylmethylideneindane-1 : 3-diones.*

By AHMED MUSTAFA.

SINCE 2-arylmethylideneindane-1 : 3-diones (I) undergo addition reactions, *e.g.*, with malonic ester in the presence of piperidine (Ionescu, *Bull. Soc. chim.*, 1925, [iv], **37**, 913; *Bul. Soc. Stiinte Cluj*, 1926, **3**, 112), the addition of thiols to a series of such diones has been investigated. When yellow 2-benzylideneindane-1 : 3-dione (I; R = Ph) and thiophenol were heated together on the water-bath without a catalyst (cf. Nicolet, *J. Amer. Chem. Soc.*, 1935, **57**, 1098), addition occurred within five minutes, to give the colourless adduct (III; R = R′ = Ph). This regenerates thiophenol and (I) at the melting point or when heated with aqueous potassium hydroxide (cf. Nicolet, *ibid.*, 1931, **53**, 3066).


(I.)


(II.)


(III.)

The products obtained could be represented by either (II) or more probably (III) (cf. Nicolet, *loc. cit.*; Ruhemann, *J.*, 1905, 461). The latter structure accords with the fact that it (III;

2-[α-*Aryl*(*or benzyl*)*thio*-α-*arylmethyl*]*indane*-1 : 3-*diones* (III).

				Found, %.				Required, %.			
R.	R′.	M. p.*	Formula.	C.	H.	N.	S.	C.	H.	N.	S.
Ph	Ph	89—90°	$C_{28}H_{22}O_2S$	76·6	4·5	—	9·1	76·8	4·6	—	9·3
Ph	*o*-Tolyl	113	$C_{29}H_{24}O_2S$	77·1	4·9	—	8·7				
Ph	*p*-Tolyl	102	,,	76·9	5·1	—	8·8	77·1	5·0	—	8·95
Ph	Benzyl	89—90	,,	77·0	4·8	—	8·6				
m-Tolyl	Ph	97—98	,,	77·0	4·9	—	8·9				
m-Tolyl	*p*-Tolyl	100—101	$C_{30}H_{26}O_2S$	77·2	5·3	—	8·4	77·4	5·4	—	8·6
p-Tolyl	Ph	84	$C_{29}H_{24}O_2S$	76·8	4·8	—	8·6	77·1	5·0	—	8·95
p-Tolyl	*o*-Tolyl	82	$C_{30}H_{26}O_2S$	77·1	5·2	—	8·3				
p-Tolyl	*p*-Tolyl	110	,,	77·4	5·1	—	8·5	77·4	5·4	—	8·6
p-Tolyl	Benzyl	76	,,	77·2	5·0	—	8·3				
o-NO_2·C_6H_4	Ph	120	$C_{28}H_{21}O_4NS$	67·5	3·7	3·6	8·1	67·8	3·9	3·6	8·2
o-NO_2·C_6H_4	*o*-Tolyl	115	$C_{29}H_{23}O_4NS$	68·3	4·0	3·1	7·6				
o-NO_2·C_6H_4	*p*-Tolyl	109	,,	68·4	4·1	3·0	7·8	68·5	4·2	3·4	7·9
o-NO_2·C_6H_4	Benzyl	111—112	,,	68·3	4·2	3·2	7·6				
m-NO_2·C_6H_4	Ph	120	$C_{28}H_{21}O_4NS$	67·6	3·7	3·4	7·9	67·8	3·9	3·6	8·2
m-NO_2·C_6H_4	*o*-Tolyl	82	$C_{29}H_{23}O_4NS$	68·4	4·1	3·0	7·7				
m-NO_2·C_6H_4	*p*-Tolyl	120	,,	68·1	4·2	3·3	7·5	68·5	4·2	3·4	7·9
m-NO_2·C_6H_4	Benzyl	99	,,	68·2	3·9	3·0	7·8				
p-NO_2·C_6H_4	Ph	118	$C_{28}H_{21}O_4NS$	67·5	3·6	3·5	8·0	67·8	3·9	3·6	8·2
p-NO_2·C_6H_4	*o*-Tolyl	119	$C_{29}H_{23}O_4NS$	68·2	4·0	3·1	7·5				
p-NO_2·C_6H_4	*p*-Tolyl	131	,,	68·1	4·1	3·0	7·4	68·5	4·2	3·4	7·9
p-NO_2·C_6H_4	Benzyl	139	,,	68·0	4·0	3·4	7·6				
p-C_6H_4Cl	Ph	110	$C_{28}H_{21}O_2ClS$ [1]	69·4	3·6	—	8·0	69·7	3·9	—	8·4
p-C_6H_4Cl	*o*-Tolyl	108	$C_{29}H_{23}O_2ClS$ [2a]	69·9	4·0	—	7·8				
p-C_6H_4Cl	*p*-Tolyl	111	,, [2b]	70·1	4·1	—	8·1	70·3	4·3	—	8·1
p-C_6H_4Cl	Benzyl	83	,, [2c]	69·9	3·9	—	8·0				

* With decomp. [1] Found : Cl, 8·9. Reqd. : Cl, 9·4%. [2] Found : Cl (*a*) 7·8, (*b*) 8·1, (*c*) 8·0. Reqd. : Cl, 9·0%.

The compounds were recrystallised from light petroleum (b. p. 40—60°). In cold, concentrated sulphuric acid they give deep green solutions, which when heated on the water-bath develop the colour acquired by the corresponding 2-arylmethylideneindane-1 : 3-dione when the latter is treated with cold sulphuric acid. They are colourless, except that the nitro-compounds are very pale yellow.

R = R′ = Ph) dissolves in cold, aqueous ammonia with an orange-red colour (owing to enolisation; cf. the purplish-red colour of 1 : 2-diphenylindenone); neutralisation with ice-cold, dilute hydrochloric acid liberates (III; R = R′ = Ph).

o- and *p*-Thiocresol and toluene-ω-thiol give similar adducts (cf. Table).

EXPERIMENTAL.—*Addition of thiols to 2-arylmethylideneindane-1 : 3-diones.* Equimolecular quantities of the reactants were heated for 5 minutes on the steam-bath, a clear solution being obtained. The solution was shaken quickly with excess of light petroleum (b. p. 40—60°) and filtered. On cooling, the filtrate gave an almost quantitative yield of the adduct.

Thermal decomposition. The adduct (1 g.), *e.g.*, (III; R = R′ = Ph), was heated in an oil-bath (bath-temp., 120°) in a stream of dry carbon dioxide for 20 minutes. The cooled melt was extracted with light petroleum (b. p. 30—50°), the extract was evaporated, and the oily residue treated with benzoyl chloride in the presence of sodium hydroxide; colourless crystals were obtained which, after recrystallisation from ethyl alcohol, proved to be phenyl thiolbenzoate (m. p. and mixed m. p.) (Found: C, 72·6; H, 4·9; S, 14·9. Calc. for $C_{13}H_{10}OS$: C, 72·9; H, 4·7; S, 14·9%). The part insoluble in light petroleum was crystallised from benzene in yellow crystals, m. p. 151°, and proved to be 2-benzylideneindane-1 : 3-dione (m. p. and mixed m. p., and colour reaction with sulphuric acid).

When the addition compounds obtained from *o*-thiocresol or toluene-ω-thiol were thermally decomposed, the thiols obtained were identified as the corresponding disulphides. *p*-Thiocresol was identified as its benzoyl derivative (m. p. and mixed m. p.).

Alkaline hydrolysis. To a solution of the adduct, *e.g.* (III; R = R′ = Ph), in alcohol (50 c.c.) was added 5% aqueous potassium hydroxide (10 c.c.), and the mixture heated on a boiling water-bath for 10 minutes. After cooling, it was neutralised with cold, dilute hydrochloric acid and extracted with ether, the extract being dried and evaporated. The oily residue was treated with light petroleum (b. p. 30—50°); the soluble part proved to be thiophenol (cf. above), and the insoluble part was the dione.

CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE,
FOUAD I UNIVERSITY, ABBASSIA-CAIRO, EGYPT. [*Received, January 2nd*, 1951.]

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308. *The Catalytic Hydrogenation of Diphenyl in the Presence of Raney Nickel.*

By ISAAC GOODMAN.

THE earliest studies of the catalytic hydrogenation of diphenyl were those by Eykman (*Chem. Weekblad.*, 1903, 7) and Sabatier and Murat (*Ann. Chim.*, 1915, **4**, 253). Eykman succeeded only in obtaining the hexahydro-compound, but the latter investigators prepared dodecahydrodiphenyl (di*cyclo*hexyl) by repeated passage of diphenyl vapour with hydrogen over a nickel catalyst. In a subsequent investigation by Kagehira (*Bull. Chem. Soc., Japan*, 1931, **6**, 241), di*cyclo*hexyl was obtained as the primary hydrogenation product at 80—200°, but at higher temperatures dehydrogenation (so-called "partial oxidation") occurred, giving phenyl*cyclo*hexane. The platinum-oxide-catalysed hemihydrogenation of various compounds containing two benzene nuclei has been studied by Smith, Alderman, Shacklett, and Welch (*J. Amer. Chem. Soc.*, 1949, **71**, 3772) who found that, whilst diphenylmethane and *as*-diphenylethane could be uniquely converted into the phenyl*cyclo*hexyl analogues, diphenyl gave a mixed product containing only 60% of phenyl*cyclo*hexane. None of these methods offers a convenient procedure for the selective hydrogenation of diphenyl, and indeed the hemihydrogenation product has been more easily obtained by the *cyclo*hexylation of benzene, although considerable by-product formation occurs (*Org. Synth.*, Coll. Vol. **2**, p. 151). The catalytic hydrogenation, in suitable conditions, of diphenyl has now given phenyl*cyclo*hexane and di*cyclo*hexyl separately in good yield and substantially free from one another.

A study of the hydrogenation curves (pressure–time) in falling-pressure experiments indicated the occurrence at different temperatures of three distinct processes. Rapid hydrogenation to di*cyclo*hexyl occurred only at 200°, giving high yields. The other processes were the rapid partial hydrogenation to phenyl*cyclo*hexane, followed by the slower hydrogenation of this to di*cyclo*hexyl. At 160°, for example, the curve showed an initial rapid reaction upon which was superimposed the less rapid, but still considerable, rate of further hydrogenation.

These conditions were still not specific for the hemihydrogenation of diphenyl, and the reaction temperature was therefore reduced to 100°, and finally to 80°. When, in these conditions, the hydrogenation was allowed to proceed until no further absorption was observed, it was still found that some overhydrogenation (*i.e.* more than the 3 moles of hydrogen per mole

of diphenyl) had occurred; this excessive absorption appeared to occur in the relatively long period between the end of the first, rapid pressure drop and the complete cessation of absorption. Interruption of the reaction at the end of the first period, and distillation of the product, gave a high yield of phenyl*cyclo*hexane whose purity was established by comparison with a sample obtained by desulphonation of sodium *p-cyclo*hexylbenzenesulphonate.

It is interesting that hydrogenation of phenyl*cyclo*hexane occurs, albeit slowly, even at 80°. In the hydrogenation of fluorene, whose reactivity in many respects resembles that of diphenyl, it has not been found possible to interrupt the reaction at the hexahydro-stage, and perhydrogenation here appears even more prominent.*

Experimental.—Preparation of dicyclohexyl. Diphenyl (100 g.), ethanol (80 c.c.), and Raney nickel (10 g.) were shaken in a stainless-steel autoclave with hydrogen [initial (cold) pressure, 1450 lbs./sq. in.]. Hydrogenation was continued for 15 hours at 200°, whereupon the pressure was steady. The product was freed from alcohol by distillation, and the di*cyclo*hexyl washed with concentrated sulphuric acid to remove any aromatic component. Distillation then gave di*cyclo*hexyl (100 g., 92·5%), b. p. 235—239°/767 mm., n_D^{20} 1·4849, $d_4^{21\cdot5}$ 0·885. The observed pressure drop in this experiment corresponded to 5·88 moles of hydrogen per mole of diphenyl (98%).

*Preparation of phenyl*cyclo*hexane.* Diphenyl (20 g.), ethanol (16 c.c.), and Raney nickel (4 g.) were shaken at 100° with hydrogen (initial pressure 900 lbs./sq. in. at 20°). The reaction was interrupted after 3½ hours; the observed pressure drop corresponded to an uptake of 2·89 moles of hydrogen per mole of diphenyl (96·4%). Distillation of the product gave phenyl*cyclo*hexane (18 g., 86·7%), b. p. 100—102°/15 mm., n_D^{20} 1·5217. Desulphonation of the sodium sulphonate gave a product, b. p. 103—105°/12 mm., n_D^{20} 1·5236.

Uninterrupted hydrogenation at 80° and 100°. Diphenyl was hydrogenated as in the previous experiment until no further pressure drop occurred. The products were distilled, and their compositions determined from the refractive indices. In all cases, formation of significant quantities of di*cyclo*hexyl had occurred.

			Product.		
Temp.	Reaction time, hrs.	Absorption.*	B. p.	n_D^{20}.	Di*cyclo*hexyl, %.
100°	11·5	3·23	99—108°/10 mm.	1·5157	20
100	8	3·2	230—236°/760 mm.	1·5142	23
80	8·5	3·17	93—100°/15 mm.	1·5152	21

* Moles of hydrogen per mole of diphenyl.

PETROCARBON, LTD., RESEARCH LABORATORIES,
TWINING ROAD, MANCHESTER, 17.

[*Received, November 24th*, 1950.]

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309. *Phormium Gum.*

By R. J. MCILROY.

A PRELIMINARY examination (McIlroy, *N.Z.J. Sci. Tech.*, **1944**, **26**, *B*, 161) of the gum exuded from the leaves of *Phormium tenax* indicated that it is a polysaccharide composed of D-glucuronic acid, a pentose, and possibly D-glucose. The aqueous solution of the gum was neutral, non-reducing, and lævorotatory ($[\alpha]_D^{14}$ −63°). The equivalent by titration was 880.

Proximate analysis of the purified gum by the usual methods indicated the following composition: uronic anhydride, 42·4 (carbon dioxide 10·6%); anhydropentose, 45·0 (furfuraldehyde 37·0%); apparent lignin, 3·8; ash, 5·0%.

The reducing sugar obtained on hydrolysis was converted quantitatively into dibenzylidene D-xylose dimethylacetal, m. p. and mixed m. p. 212° (Breddy and Jones, *J.*, 1945, 738; Wise and Ratliff, *Ind. Eng. Chem. Anal.*, 1947, **19**, 694). This indicates that D-xylose is the only sugar present; phormium gum is thus a polyuronide constituted of D-xylose and D-glucuronic acid residues, and is comparable to Phormium hemicellulose (McIlroy, Holmes, and Mauger, *J.*, 1945, 796; McIlroy, *J.*, 1949, 121).

On periodate oxidation the gum consumed 1·7 mols. of periodate per anhydroxylose unit, compared with xylan which consumed 1·2 mols. of periodate (Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1296). The periodate consumption indicates a predominance of α-glycol residues in

* I am indebted to one of the Referees for drawing my attention to the work of Idris Jones and Lindsey (*J.*, 1950, 1836) on the Raney-nickel-catalysed hydrogenation at 200° of a dihydroxydiphenyl and diphenylene oxide. In both cases, hemireduction gave only limited yields of the hexahydro-compounds, together with hydrogenolysis products and unhydrogenated material. The two compounds are thus more resistant to controlled hydrogenation than are the hydrocarbon analogues.

the xylose chain, as in xylan. The greater consumption of periodate by the gum is, no doubt, due to the presence of uronic acid. A terminal residue of uronic acid consumes at least 2 mols. of periodate and possibly more on over-oxidation. These results are in agreement with either 1 : 2- or 1 : 4-linkages, although the latter, by analogy with xylan and hemicellulose, are more probable.

Phormium gum was extremely resistant to methylation and was degraded in the process. Methyl sulphate and sodium hydroxide in aqueous acetone (six treatments) followed by methyl iodide–silver oxide (three treatments) gave a product (OMe 28·6%; yield 6%). Attempts to prepare a more highly methylated gum by the thallous hydroxide–methyl iodide method were unsuccessful.

Experimental.—Purification of the gum. The crude gum collected from *Phormium tenax* var. S.S., grown on the Moutoa Estate, Foxton, N.Z., was dissolved in hot water, and the hot solution filtered through glass wool. Addition of an equal volume of 95% alcohol to the cooled solution, after acidification with glacial acetic acid, precipitated the gum as a colourless, ropy coagulum which was separated by vacuum filtration on cloth and washed free from acid. The viscous crude gum (642 g.) yielded 63 g. of dried, purified product (ash, 5·0%).

Estimation of uronic anhydride. The purified gum (10 mg.) was heated with 12% hydrochloric acid saturated with sodium chloride for 3·5 hours at 135—137° (bath temp.) (Burkhart, Baur, and Link, *J. Biol. Chem.*, 1934, **104**, 171). 10·6% of carbon dioxide, corresponding to 42·4% (10·6 × 4) of uronic anhydride was produced.

Estimation of xylose. The purified gum (1·02 g.; ash, 5·6%) was hydrolysed with 3% sulphuric acid for 21 hours at 100° {final rotation, $[\alpha]_D^{13}$ +50° (c = 1)}. The solution, neutralised by barium carbonate, was evaporated to dryness and the free sugars extracted with boiling alcohol. The material (0·39 g.) obtained on evaporation of the extracts was treated with Breddy and Jones's reagent (*loc. cit.*), and gave a quantitative yield of dibenzylidene xylose dimethylacetal, m. p. and mixed m. p. 212°, indicating that xylose is the only sugar present.

Heating of the gum with 18·5% hydrochloric acid gave furfuraldehyde (37%; 72·8% phloroglucide precipitate), a portion of which is derived from uronic anhydride. Uronic anhydride yields 21·48% of furfuraldehyde under these conditions. The anhydroxylose content (45·0%) was calculated by use of Angell, Norris, and Resch's formula (*Biochem. J.*, 1936, **30**, 2146).

Periodate oxidation. Duplicate samples of dry, purified gum (200 mg.) (ash 5%) in water (20 c.c.) were oxidised (Halsall, Hirst, and Jones, *J.*, 1947, 1430; Jeanes and Wilham, *J. Amer. Chem. Soc.*, 1950, **72**, 2657) with an excess of sodium metaperiodate (25 c.c.; 0·298M.) at 25°. The amount of periodate consumed (mols. per $C_5H_8O_4$ unit) was determined by Fleury and Lange's method (*J. Pharm. Chim.*, 1933, **17**, 107, 196): 1·75 (50 hrs.); 1·72 (74 hrs.); 1·80 (100 hrs.). A sample (198·4 mg.) of esparto xylan oxidised under identical conditions at the same time consumed periodate (mols. per $C_5H_8O_4$ unit): 1·20 (50 hrs.); 1·21 (74 hrs.); 1·21 (100 hrs.). These results are in close agreement with those obtained for esparto xylan by Chanda, Hirst, Jones, and Percival (*loc. cit.*).

UNIVERSITY COLLEGE, IBADAN, NIGERIA. [*Received, January 17th*, 1951.]

310. *The Dehydrogenation of* 1 : 2 : 3 : 4-*Tetrahydrocarbazole.*

By W. E. BADCOCK and K. H. PAUSACKER.

1 : 2 : 3 : 4-TETRAHYDROCARBAZOLE has been dehydrogenated, forming carbazole, by (*a*) distillation over lead oxide (Borsche, Witte, and Bothe, *Annalen*, 1908, **359**, 74), (*b*) sulphur in boiling quinoline (Perkin and Plant, *J.*, 1923, **123**, 694), (*c*) palladised charcoal in a stream of hydrogen at *ca.* 300° (Pausacker and Schubert, *J.*, 1949, 1387), (*d*) palladised charcoal in boiling xylene (Horning, Horning, and Walker, *J. Amer. Chem. Soc.*, 1948, **70**, 3935), (*e*) fusion with palladium and cinnamic acid (Hoshino and Takiura, *Bull. Chem. Soc. Japan*, 1936, **11**, 218), and (*f*) chloranil in boiling xylene (Barclay and Campbell, *J.*, 1945, 530).

It has now been found that when a xylene solution is refluxed in the presence of Raney nickel, carbazole is formed in theoretical yield along with the evolution of almost two moles of hydrogen. Light petroleum (b. p. 100—120° or 70—90°) may also be used as a solvent, but the yields were lower (91 and 52% respectively). When *cyclo*hexanone was added, carbazole was again obtained in theoretical yield, *cyclo*hexanol (30% yield, isolated as its 3 : 5-dinitrobenzoate) also being formed. Kleiderer and Kornfeld (*J. Org. Chem.*, 1948, **13**, 455) have also used this method for oxidising alcohols to carbonyl compounds. However, the presence of hydrogen acceptors, other than *cyclo*hexanone, caused a decrease in yield. Thus, under the same conditions, the acceptors and yields are: phenyl*cyclo*hexene (73%), benzophenone (65%), fluorenone (59%), and cinnamic acid (31%).

The method does not appear to be general, as 3-chloro- and 3-nitro-carbazole could not be isolated when 6-chloro-1 : 2 : 3 : 4-tetrahydro- and 1 : 2 : 3 : 4-tetrahydro-6-nitro-carbazole were treated with Raney nickel in xylene. In addition, it was found that tetralin was converted

into naphthalene (isolated as its picrate, 13%), although decalin is unchanged (cf. Paul, *Bull. Soc. chim.*, 1940, **7**, 334).

Experimental.—Sulphur-free xylene (60 ml.) was added to Raney nickel (5 ml.), and 10 ml. were distilled off to remove any alcohol. 1 : 2 : 3 : 4-Tetrahydrocarbazole (4·3 g.) was added and the mixture refluxed for 6 hours. After filtration of the hot solution, the xylene was removed *in vacuo* and the residue sublimed, yielding carbazole (4·2 g.; m. p. 235°).

Quantitative runs were performed by first boiling the alcohol-free Raney nickel in xylene until hydrogen evolution ceased and then adding the compound to be dehydrogenated. The following results were obtained, the figures in parentheses representing the wt. of substance (g.), volume of hydrogen (ml.), and percentage of theoretical volume: tetrahydrocarbazole (3·8, 1140, 96); 6-chloro-1 : 2 : 3 : 4-tetrahydro- (3·0, 80, 18) and 1 : 2 : 3 : 4-tetrahydro-6-nitro-carbazole (3·0, 40, 6·2); 1 : 2 : 3 : 4-tetrahydro-11-methylcarbazolenine (3·0, 74, 17); and tetralin (1·9, 250, 45). The rate of evolution of hydrogen from tetrahydrocarbazole appeared to follow a first-order sequence ($k = 5 \times 10^{-4}$ sec.$^{-1}$).

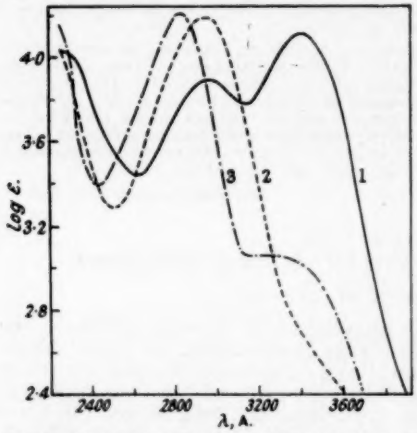
UNIVERSITY OF MELBOURNE, N.3, VICTORIA, AUSTRALIA. [*Received, January 18th*, 1951.]

311. *The Structure of 4-Pyridthione.*

By I. G. ROSS.

CHEMICAL and physical measurements, especially those by Specker and Gawrosch (*Ber.*, 1942, *B*, **75**, 1338), on the compound obtained by inserting a hydroxyl group in the 4-position of pyridine have shown that it is undoubtedly to be formulated as 4-pyridone (I; X = O). No corresponding examination has been recorded of its sulphur analogue, which may be either 4-pyridthione (I; X = S), pyridine-4-thiol (IV; X = S), or a tautomeric mixture of both.

The sulphur analogue is a pale yellow solid, freely soluble in hydroxylic solvents, giving a yellow solution which is decolorised by the addition of either acid or alkali. The absorption spectra in various media have now been measured, and details are given in the figure and the table; in the latter f is the oscillator strength, calculated from the formula, $f = 4{\cdot}31 \times 10^{-9} \int \epsilon d\nu$, where ν is the frequency in cm.$^{-1}$.



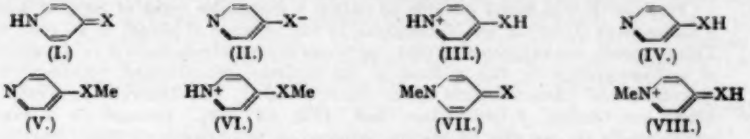
Spectra of 4-pyridthione. 1. *In ethanol.* 2. *In* 0·1N-*ethanolic ammonia.* 3. *In* 0·1N-*ethanolic hydrogen chloride.*

The discussion of these spectra must be made in conjunction with those of 4-pyridone, and the spectra of this compound have therefore been measured in the same media; the data obtained are included in the table, but the curves themselves differ so little (apart from a small wave-length shift) from those obtained in methanol solution by Specker and Gawrosch (*loc. cit.*) that their separate presentation is unnecessary. The table lists the principal band systems observed, together with their tentative assignments to the various molecular and ionic species whose existence in the solution must be considered; the assignments for pyridone and its derivatives are those by Specker and Gawrosch, except for (VIII), the nature of the band concerned having been left an open question by these authors.

The fact that the absorption of quinonoid 4-pyridone (I) does not resemble that of *p*-benzoquinone is in keeping with the fact that *p*-benzoquinoneimine is also colourless; the 3410-A. band in 4-pyridthione is also attributed to a quinonoid structure, the frequency shift (−9740 cm.$^{-1}$) being in keeping with the quasi-classical theory of light absorption advanced by Lewis and Calvin (*Chem. Reviews*, 1939, **25**, 273). An alternative possibility, that it is due to a singlet–triplet transition, localised within the C:S group, such as occurs in diphenylthione (Lewis and Kasha, *J. Amer. Chem. Soc.*, 1945, **67**, 994), may be discounted by applying Lewis and Kasha's criteria for such bands; in particular, the wave-length is rather too short, and the intensity, for a spin-forbidden transition, far too great.

Albert and Short (*J.*, 1945, 760) have observed that 2- and 4-acridone exist in the tautomeric hydroxy-forms in solvents of low dielectric constant; it might be expected that, similarly, the

benzenoid form (IV) of pyridthione could be detected in hexane solution. The substance is, however, almost insoluble in *n*-hexane. Nevertheless, a saturated solution (2 cm. path) did show an unmistakable band at 2350 A. (maximum extinction 0·22), together with about 2% absorption between 2700 and 3300 A. This band has no parallel in the spectra shown in the figure, and may well be attributable to (IV); it must then be regarded as shifting to 2600 A. on *S*-methylation (V; X = S). It may be noted that a large shift also occurs on *S*-methylation of thiophenol (2360 to 2540 A.) (Koch, *J.*, 1949, 391; Fehnel and Carmack, *J. Amer. Chem. Soc.*, 1949, **71**, 84). A comparable band could not be observed in 4-pyridone, a saturated *n*-hexane solution of which shows no measurable absorption at wave-lengths down to 2200 A.



Absorption bands of 4-pyridone and 4-pyridthione.

	X = O.				X = S.			
Solute.	Solvent.	$\lambda_{max.}$	log $\varepsilon_{max.}$	*f*.	Solvent.	$\lambda_{max.}$	log $\varepsilon_{max.}$	*f*.
(I)	EtOH	2560	4·16	0·26	EtOH	3410	(4·11)	(0·19)
(II)	EtOH + NaOEt	2430	4·05	0·22	EtOH + NH_3	2950	4·18	0·28
		2600*S*	3·85					
(III)	EtOH + HCl	2350	3·99	0·18	EtOH + HCl	2825	4·20	0·26
(IV)	—	—	—	—	C_6H_{14}	2350	—	—
(V)	MeOH [b]	2180	3·9	—	EtOH [b]	2600	4·2	—
		2450*S*	3·0	—				
(VI)	MeOH + HCl [a]	2400	4·1	—				
(VII)	MeOH [b]	2600	4·2	—				
(VIII)	MeOH + HCl [a]	2370	4·0	—				

(*a*) Specker and Gawrosch, *loc. cit.*; (*b*) Welsh, unpublished measurement (Thesis, Sydney, 1946). *S* denotes an unresolved shoulder.

Experimental.—4-Pyridone and 4-pyridthione were prepared by King and Ware's methods (*J.*, 1939, 873); 4-pyridone was vacuum-distilled, and obtained as lustrous plates, m. p. 149°, after two crystallisations from acetone (charcoal); 4-pyridthione was recrystallised several times from methanol containing a little ethanol (charcoal), and then had m. p. 184°.

The absorption spectra were measured with a Cary recording spectrophotometer.

I am indebted to Mr. A. Boden, Hardman Research Laboratory, Sydney, for a gift of chemicals; to Mr. F. Walker for carrying out some of the preparative work; and to Dr. D. P. Craig for discussions on this work, which was carried out during the tenure of an Australian National University Scholarship.

William Ramsay and Ralph Forster Laboratories,
University College, London, W.C.1. [*Received, January 31st*, 1951.]

312. *The Preparation of* 1-*Bromo*-2-*methylnaphthalene.*

By D. Muriel Hall and R. K. Mitchell.

1-Bromo-2-methylnaphthalene has been obtained by monobromination of 2-methylnaphthalene in carbon disulphide by Schulze (*Ber.*, 1884, **17**, 1527), Mayer and Sieglitz (*Ber.*, 1922, **55**, 1835; 70% yield; b. p. 165—170°/13 mm.), and others (*e.g.*, Fuson, McKeever, and Behr, *J. Amer. Chem. Soc.*, 1941, **63**, 2648; 92% yield; b. p. 125—129°/5 mm.). Adams and Binder (*J. Amer. Chem. Soc.*, 1941, **63**, 2773) used carbon tetrachloride as solvent, with iodine and iron powder as catalysts and with the exclusion of light; they added the bromine (160 g.) in carbon tetrachloride solution during 8 hours, with mechanical stirring and at >5°; they obtained an 84% yield and b. p. 152—156°/14 mm.

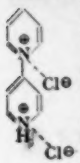
We now find that, by using the quantities and conditions of Adams and Binder (*loc. cit.*) but adding the bromine solution during 15 minutes and continuing the stirring for a further 40 minutes before adding aqueous sodium hydroxide, we obtain an 87% yield and b. p. 112—117°/1 mm. From 142 g. of 2-methylnaphthalene the average yield from five preparations is 193 g. (87%).

Bedford College, London. [*Received, February 2nd*, 1951.]

313. 4-*Aminopyridine.*

By Adrien Albert.

It has been claimed that 4-aminopyridine can be prepared in 60% yield by heating 1-4′-pyridylpyridinium chloride hydrochloride (I) with aqueous ammonia at 150° (Koenigs and Greiner, *Ber.*, 1931, **64**, 1052). Experience has shown that this reaction often fails and for this reason it has been suggested by Mosher (Elderfield's "Heterocyclic Compounds," 1950, Vol. I, p. 552, Wiley, New York) that 4-aminopyridine should preferably be prepared from 4-picoline *via* the Curtius or Hofmann degradation of pyridine-4-carboxylic acid.



(I.)

However it was found possible to obtain a repeatable yield of 80% of 4-aminopyridine from (I) by the use of ammonia, in the presence of phenol, in an open vessel. This approach was suggested by many previous successful experiences in the amination of γ-chloro-groups by this method in the acridine, benzacridine, quinoline, benzoquinoline, and phenanthroline series (Albert, Brown, and Duewell, *J.*, 1948, 1284; Albert and Gledhill, *J. Soc. Chem. Ind.*, 1945, **64**, 169). Because (I) is available commercially (it can also be readily prepared in the laboratory from pyridine and thionyl chloride) this one-stage method offers a distinct advantage over the suggested preparation from 4-picoline which is not readily obtained pure.

Experimental.—The salt (I) was prepared by Koenigs and Greiner's method (*loc. cit.*) and purified by dissolving each gram in 0·5 ml. of boiling 0·1N-hydrochloric acid, filtration from colloidal material, treatment with charcoal, re-filtration, and evaporating to crystallizing point. This hot solution was diluted with an equal volume of absolute alcohol and kept at −4° for a day; then the white crystals were filtered off (80% recovery; m. p. 171—173°). The yield was 50% based on pyridine taken.

Purified (I) (14·6 g.) and phenol (58·5 g.) were heated under reflux in a bath at 180—190° while ammonia was passed at 2—3 bubbles per second for 3 hours. The method of isolation was devised from knowledge that 4-aminopyridine is highly hydrophilic and a strong base (pK_a 9·2). The partition coefficient between chloroform and water was found to be about 0·2, and the solubility in chloroform at 20° was about 1 in 40 (about 1 in 20 at the boil) and in water at 20° it was about 1 in 12.

The flask was cooled, water (20 ml.) added, and the pH adjusted to 7 with a little N-hydrochloric acid. The contents were then distilled in steam (to remove phenol), readjusted to pH 7 with a little 10N-sodium hydroxide, and evaporated to a paste which was stirred with 10N-sodium hydroxide (about 10 ml. or enough to redden Tropaeolin OOO, *i.e.*, pH *ca.* 12). The mixture was filtered through a No. 54 Whatman paper. The filter-cake was well pressed, then transferred to porous tile to drain, while the filtrate was extracted with chloroform (75 + 75 + 75 ml.). The filter-cake was then extracted with boiling chloroform (120 + 100 + 50 ml.). The combined extracts were concentrated to 10 ml., giving 4·8 g. (80%) of 4-aminopyridine, m. p. 155—158°. Recrystallization, by continuous extraction with benzene (50 ml.), gave white crystals (90% recovery), m. p. 158°, which is the highest melting point recorded.

Department of Medical Chemistry, The Australian National University,
183 Euston Road, London, N.W.1. [*Received, February 16th*, 1951.

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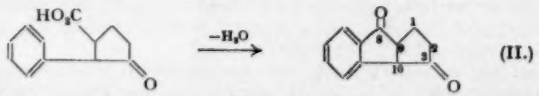
314. *Fluorosulphonic Acid as a Cyclodehydrating Agent.*

By Wilson Baker, G. E. Coates, and F. Glockling.

Unsuccessful attempts to effect the cyclisation of 3-keto-2-phenyl*cyclo*pentane-1-carboxylic acid (I) to 1 : 2 : 3 : 8 : 9 : 10-hexahydro-3 : 8-diketo*cyclo*pent[*a*]indene (II) (Baker and Jones, *J.*, 1951, 789) by a variety of standard methods, including the use of polyphosphoric acid (see Baker and Leeds, *J.*, 1948, 974; Snyder and Werber, *J. Amer. Chem. Soc.*, 1950, **72**, 2962, 2965), led us to investigate the possibility of using fluorosulphonic acid, $F{\cdot}SO_2{\cdot}OH$, for this purpose. It was found that fluorosulphonic acid reacted smoothly with (I) at room temperature, giving the desired diketone (II) in high yield. Details of this experiment will be reported later.



In view of this successful reaction, fluorosulphonic acid, which is now commercially available, was used to effect the cyclodehydration of several aromatic acids to cyclic ketones. The results, tabulated below, show that very satisfactory yields of the ketones were obtained. β-Phenylpropionic acid gave, in addition to indan-1-one, a small quantity of the dimeric anhydroderivative, 2-1′-indanylideneindan-1-one. δ-Phenylvaleric acid gave no 1 : 2-benzo*cyclo*hepten-

3-one (benzsuberone) under the conditions employed, and extensive fluorosulphonation occurred. As a cyclodehydrating agent, fluorosulphonic acid has the advantage over hydrogen fluoride in that the reactions may be carried out in glass apparatus, although slight etching does occur. It is, moreover, less prone to form tarry by-products than some other cyclising agents. For a successful cyclisation, however, the conditions must be sufficiently vigorous to bring about cyclodehydration, but not such as will cause fluorosulphonation or sulphonation of either the starting material or the cyclic ketone. As the aromatic nucleus of the cyclic ketone is partly deactivated by the ketonic group, substitution is less likely to occur than in the original acid. For the same reason cyclisation of the acid is unlikely to occur if it has undergone previous fluorosulphonation or sulphonation, and it is therefore improbable that fluorosulphonic acid can be used for the cyclisation of acids possessing reactive aromatic nuclei, *e.g.* if they contain methoxyl or substituted amino-groups. The optimum conditions for cyclodehydration with fluorosulphonic acid require study in each particular case, and this reagent is likely to prove of greatest use where other methods of cyclisation fail, *e.g.* in the conversion of (I) into (II).

Acid.	Temp.	Time (hrs.).	Product.	Yield (%).
β-Phenylpropionic	100°	1½	Indan-1-one	68
γ-Phenylbutyric	15	5	α-Tetralone	61
Phenylsuccinic	100	1½	3-Ketoindane-1-carboxylic acid	77
o-Benzoylbenzoic	100	3	Anthraquinone	86

Fluorosulphonic acid has previously been used as a catalyst and as a fluorosulphonating or sulphonating agent (Steinkopf, *J. pr. Chem.*, 1927, **117**, 1; Langer and Müller, *Ber.*, 1930, **63**, 2653; Renoll, *J. Amer. Chem. Soc.*, 1942, **64**, 1489; Simons, Passino, and Archer, *ibid.*, 1941, **63**, 608), and its esters have also been investigated (Meyer and Schramm, *Z. anorg. Chem.*, 1932, **206**, 24). Adipic, suberic, and benzoic acids were unaffected by fluorosulphonic acid at room temperature; the first and last were also unchanged at 100°. Phenylacetic acid gave *p*-fluorosulphonylphenylacetic acid in high yield.

Experimental.—Indane-1-one and 2-1′-Indanylideneindan-1-one. β-Phenylpropionic acid (15 g.) and fluorosulphonic acid (16 c.c.) were heated on the steam-bath for 1½ hours, cooled, and poured into water, and the orange-brown oil extracted into ether. The ethereal extract, after addition of aqueous sodium carbonate, was steam-distilled and the distillate yielded pure indan-1-one (8·9 g.), m. p. 42° (lit., m. p. 39—41°). The cooled alkaline solution was filtered, giving 2-1′-indanylideneindan-1-one (0·35 g.) as pale yellow needles, m. p. 145°. Kipping (*J.*, 1894, **65**, 495) records m. p. 142—143° (Found, in material crystallised three times from ethanol: C, 88·1; H, 5·9. Calc. for $C_{18}H_{14}O$: C, 87·8; H, 5·7%). Acidification of the alkaline solution gave a trace of β-phenylpropionic acid.

α-Tetralone. γ-Phenylbutyric acid (10 g.) and fluorosulphonic acid (25 c.c.) were kept at room temperature for 5 hours, and the product was isolated as in the previous case, giving α-tetralone (5·4 g.), b. p. 79°/0·3 mm. The 2 : 4-dinitrophenylhydrazone had m. p. 255° (lit., m. p. 257°).

3-Ketoindane-1-carboxylic acid. Phenylsuccinic acid (12·8 g.) and fluorosulphonic acid (28 c.c.) were heated on the steam-bath for 1½ hours. The cooled mixture was poured into water (400 c.c.), heated to boiling, and treated with charcoal. The hydrated 3-ketoindane-1-carboxylic acid, m. p. 84°, which separated, was collected and dehydrated *in vacuo*, whereafter it had m. p. 118—119° (Baker and Leeds, *J.*, 1948, 980, record m. p. 120°).

Anthraquinone. *o*-Benzoylbenzoic acid (8·7 g.) and fluorosulphonic acid (25 c.c.) were heated on the steam-bath for 3 hours, cooled, poured into water, and the solid collected and dried (7·35 g.). Crystallisation from benzene gave anthraquinone (6·9 g.), m. p. and mixed m. p. 278°.

Reaction between δ-phenylvaleric acid and fluorosulphonic acid. δ-Phenylvaleric acid (0·50 g.) and fluorosulphonic acid (3 c.c.) were mixed with cooling and after 4 hours the mixture was poured into water and extracted with ether. The ether yielded colourless needles (0·57 g.) of *δ-p-fluorosulphonylphenylvaleric acid*. After two crystallisations from benzene–light petroleum (b. p. 60—80°) it had m. p. 129—130° (Found: C, 50·5; H, 5·0. $C_{11}H_{13}O_4FS$ requires C, 50·7; H, 5·0%). The *amide*, prepared by reaction with strong aqueous ammonia, separated from water in colourless plates, m. p. 142—144° (Found: C, 50·9; H, 5·6; N, 5·5; S, 12·5. $C_{11}H_{15}O_3NS$ requires C, 51·4; H, 5·8; N, 5·4; S, 12·4%).

p-Fluorosulphonylphenylacetic acid. Phenylacetic acid (15 g.) and fluorosulphonic acid (40 c.c.) were heated at 100° for 6 hours. After the mixture had been cooled and poured into water the solid was collected, washed with cold water, and dried (yield, 11·5 g.). Crystallisation first from benzene and then from water (charcoal) gave *p-fluorosulphonylphenylacetic acid* as colourless needles, m. p. 140° (Found: C, 44·0; H, 3·2. $C_8H_7O_4FS$ requires C, 44·1; H, 3·2%). The *amide*, prepared by reaction with strong aqueous ammonia, separated from water in colourless plates, m. p. 182° (Stewart, *J.*, 1922, **121**, 2561, records m. p. 176°; the specimen was not analysed) (Found: C, 45·0; H, 4·2; N, 6·8; S, 15·4. $C_8H_9O_4NS$ requires C, 44·7; H, 4·2; N, 6·5; S, 14·9%).

The authors are grateful to the Department of Scientific and Industrial Research for a grant (awarded to F. G.), and to the Imperial Smelting Corporation, Limited, Avonmouth, for a gift of fluorosulphonic acid.

THE UNIVERSITY, BRISTOL. [*Received, February 16th*, 1951.]

315. *Sulphonium Derivatives of* DL-*Methionine and* 5-(2-*Methylthioethyl*)*hydantoin.*

By R. O. Atkinson and F. Poppelsdorf.

Toennies and Kolb (*J. Amer. Chem. Soc.*, 1945, **67**, 849) prepared a few methylsulphonium halides from methionine, and studied some of the factors governing their formation. They carried out the reactions in formic acid containing varying, but small, amounts of acetic acid and water, and concluded that the reaction is increasingly favoured in the order of increasing dielectric constant of the medium (cf. Bost and Everett, *ibid.*, 1940, **62**, 1752). They prepared methionine-methylsulphonium iodide (I) and bromide, but failed to obtain the chloride in a crystalline form.

(I.) $[R{\cdot}SMe_2]^+I^-$ $[R{\cdot}SMe_2]^+MeSO_4^-$ (II.)

$R = HO_2C{\cdot}CH(NH_2){\cdot}CH_2{\cdot}CH_2{-}$ or $NH{\cdot}CO{\cdot}CH{\cdot}CH_2{\cdot}CH_2{-}$ (CO—NH)

Recently we found that some sulphonium salts from methionine and 5-(2-methylthioethyl)-hydantoin were formed rapidly in a solely aqueous medium. Methionine-methylsulphonium iodide was prepared in 75% yield after only 6 hours at 45°, compared with 3 days at 25° in the formic–acetic acid–water medium used by Toennies *et al.* (*loc. cit.*). Methyl sulphate reacts vigorously with methionine and 5-(2-methylthioethyl)hydantoin to form the methosulphates (II) in 15 minutes in 54% and 80% yield respectively. These compounds are neutral, non-hygroscopic, and extremely soluble in water.

A procedure is described for converting the methionine methosulphate into the chloride.

Experimental.—*5-(2-Methylthioethyl)hydantoin.* Methionine (17·4 g.), sodium cyanate (17·4 g.), and water (100 c.c.) were refluxed until the solid had dissolved. Concentrated hydrochloric acid (240 c.c.) was added and heating continued for 30 minutes. The clear colourless solution was cooled to 0° overnight. The resulting solid was filtered off, recrystallised from water, and dried at 60° *in vacuo*. The yield was 16·2 g. (80%) and the m. p. 104—105° (Found : N, 16·1. Calc. for $C_6H_{10}O_2N_2S$: N, 16·2%).

Methionine-methylsulphonium iodide. Methionine (7·45 g., 0·05 mole), water (40 c.c.), and methyl iodide (7·8 g., 0·055 mole) were heated together for 6 hours at 45°. The clear solution was concentrated *in vacuo* to a thick syrup and this was triturated with hot ethanol. The salt was filtered off and recrystallised from aqueous alcohol, to give white crystals (10·4 g., 75%), m. p. 150° (decomp.) (Found : C, 24·7; H, 4·9; N, 4·7; S, 10·8; I^-, 44·0. Calc. for $C_6H_{14}O_2NSI$: C, 24·7; H, 4·8; N, 4·8; S, 10·9; I^-, 43·6%).

Methionine-ethylsulphonium iodide. Methionine (7·4 g.), water (40 c.c.), and ethyl iodide (8·6 g.) reacted as above to give the *iodide* (11·0 g., 71%), m. p. 161—162° (decomp.) (Found : C, 27·9; H, 5·1; N, 4·5; S, 10·5; I^-, 41·9. $C_7H_{16}O_2NSI$ requires C, 27·5; H, 5·2; N, 4·6; S, 10·5; I^-, 41·6%).

5-(2-Methylthioethyl)hydantoin-methylsulphonium iodide. The hydantoin (8·7 g.), water (40 c.c.), and methyl iodide (7·8 g.) reacted as above to give the *iodide* (12·8 g., 86·5%), m. p. 175° (decomp.) (Found : C, 27·9; H, 3·8; N, 9·5; S, 10·9; I^-, 42·7. $C_7H_{13}O_2N_2SI$ requires C, 28·2; H, 3·7; N, 9·4; S, 10·8; I^-, 42·9%).

Methionine-methylsulphonium (methyl sulphate). Methionine (7·45 g.) was mixed with water (10 c.c.), and methyl sulphate (6·6 g.) was added. The mixture was warmed for a few minutes on a steam-bath with occasional agitation, whereupon the pasty mass became liquid and a vigorous exothermic reaction set in. Water-cooling was used to keep the temperature below 80°. The reaction finished in 15 minutes and the product was cooled to room temperature. Ethanol (250 c.c.) was added with rapid stirring, and the precipitated *methosulphate* was filtered off and recrystallised from aqueous alcohol, the yield being 7·4 g. (54%) and the m. p. 145° (decomp.). A test for sulphate ions was negative until after hydrolysis (Found : C, 30·9; H, 5·7; N, 5·2; S, 23·7; SO_4^{2-}, 32·9. $C_7H_{17}O_6NS_2$ requires C, 30·6; H, 6·2; N, 5·1; S, 23·3; SO_4^{2-}, 34·9%).

5-(2-Methylthioethyl)hydantoin-methylsulphonium (methyl sulphate). The hydantoin (8·7 g.), water (25 c.c.), and methyl sulphate (6·6 g.) were treated as above to give the *product* (12·0 g., 80%), m. p. 168° (decomp.) (Found : C, 32·3; H, 5·3; N, 9·3; S, 21·7; SO_4^{2-}, 31·4. $C_8H_{16}O_6N_2S_2$ requires C, 32·0; H, 5·3; N, 9·3; S, 21·4; SO_4^{2-}, 32·0%).

Methionine-methylsulphonium chloride. Methionine-methylsulphonium (methyl sulphate) (14·5 g.) was heated on a steam-bath for 3 hours with concentrated hydrochloric acid (130 c.c.). The sulphate was precipitated with barium chloride and filtered off. The filtrate was concentrated to dryness *in vacuo*, dissolved in water, and neutralised with pyridine. The solution was evaporated to dryness and triturated with hot ethanol to give the *chloride* (5·1 g., 48·3%), m. p. 134° (decomp.) (Found : C, 36·1; H, 7·0; N, 6·8; S, 15·5; Cl^-, 17·5%. $C_6H_{14}O_2SNCl$ requires C, 36·0; H, 7·0; N, 7·0; S, 16·0; Cl^-, 17·7%).

We thank the Directors of the British Drug Houses Ltd. for permission to publish this work.

Amino Acids Department, The British Drug Houses Ltd.,
London, N.1.

[*Received, February 27th*, 1951.]

THE CHEMICAL SOCIETY

SCIENTIFIC MEETINGS DURING JUNE, 1951

LONDON.

Thursday, June 7th, 1951, at 7.30 p.m.

Tilden Lecture, **A Chemotherapeutic Search in Retrospect,** by Dr. F. L. Rose, O.B.E., F.R.I.C.

To be given in the Lecture Theatre, The Royal Institution, Albemarle Street, W.1.

PROCEEDINGS

OF THE

CHEMICAL SOCIETY

Minutes of a

SCIENTIFIC MEETING

held at Burlington House on Thursday, April 26th, 1951, at 7.30 p.m.

The President, PROFESSOR E. K. RIDEAL, M.B.E., M.A., D.Sc., F.R.S., was in the Chair.

MINUTES.

The Minutes of the Scientific Meeting held at Burlington House on March 20th, 1951, were read, and were confirmed and signed.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: M. Fox, I. D. Sonnenschein, O. S. Kauder, D. P. Benton, H. R. Tietze, S. R. Duff, W. W. Easton, M. L. Bird, M. Gordon, G. H. Phillipps, M. D. Potter, E. P. Taylor, F. Heyworth, K. H. Overton, E. G. Meek, M. J. Soulal, D. T. Williams, M. A. M. Graham, C. S. Woollard.

CENTENARY LECTURE.

After a brief introduction, the President called upon Professor R. B. Woodward to deliver the Centenary Lecture entitled, "Some Recent Advances in the Chemistry of Natural Products."

At the conclusion of the Lecture, a vote of thanks to Professor Woodward, proposed by Professor R. P. Linstead, was carried with acclamation.

LIST OF APPLICATIONS FOR FELLOWSHIP

(*Fellows wishing to lodge objection to the election of these candidates should communicate with the Honorary Secretaries within ten days of the date of publication of the* Journal *for May*, 1951. *Such objections will be treated as confidential. The forms of application are available in the Library.*)

***Baxter, Henry George,** A.R.C.S. British. 67, Howard Road, Walthamstow, E.17. Student, Imperial College, London. *Signed by:* R. P. Linstead, H. N. Rydon, K. R. Wooldridge.

***Bright, David Bruce,** M.S. (Illinois). American. 606, West Ohio Street, Urbana, Illinois, U.S.A. Teaching Assistant. *Signed by:* Edward C. Taylor, Nelson J. Leonard, Roger Adams.

***Buckingham, Amyand David,** B.Sc. (Sydney). British. 4, Coleridge Road, Pymble, N.S.W., Australia. Research Student. *Signed by:* R. J. W. Le Fèvre, T. Iredale, S. J. Angyal.

***Cowell, David Brian,** B.Pharm. (Lond.). British. Rakiura, Mill Park Avenue, Hornchurch. Research Student. *Signed by:* L. K. Sharp, J. B. Stenlake, A. H. Beckett.

Collier, Kenneth Arthur, B.Sc. (Lond.), A.R.I.C. British. Peek Frean & Co. Ltd., Keetons Road, Bermondsey, S.E.16. Chief Chemist. *Signed by:* A. B. Bradley, R. G. Wall, L. H. Ford.

Coyle, Denis, M.P.S. British. 46, Wellington Street, Slough. Analytical Chemist, Messrs. W. J. Bush & Co. Ltd., E.8. *Signed by:* H. Timmington, A. J. M. Bailey, J. G. Mitchell.

Eberts, Floyd Samuel, jun., M.S. (Wisconsin). American. Department of Biochemistry, University of Wisconsin, Madison, Wisconsin, U.S.A. Student. *Signed by:* W. S. Johnson, S. M. McElvain, A. L. Wilds.

El-Nawawy, Ahmed Sayed, B.Sc. (Fouad 1st Univ.). Egyptian. Department of Organic Chemistry, The University, Bristol. Research Student. *Signed by:* F. H. Pollard, W. D. Ollis, W. Baker.

Flack, Dennis Ernest John. British. 94, Windsor Road, Ilford. Research Student. *Signed by:* F. L. Allen, M. H. Tankard, J. R. Young.

***Fowler, John Denis,** B.Sc. (Sydney). British. 1, French Street, Artarmon, N.S.W., Australia. Research Student. *Signed by:* R. J. W. Le Fèvre, T. Iredale, H. C. Freeman.

***Gilham, Peter Thomas,** B.Sc. (Sydney). British. Binstead Street, Blayney, N.S.W., Australia. Student at Sydney University. *Signed by:* R. J. W. Le Fèvre, T. Iredale, J. Cymerman.

Glenn, Alan Leslie, B.Sc., B.Pharm., Ph.C. British. 3, Beverley Avenue, Hounslow. Lecturer in Pharmaceutical Chemistry, School of Pharmacy, University of London. *Signed by:* A. H. Beckett, L. K. Sharp, J. B. Stenlake.

Gooding, Frank Henry George. British. Garland Hill, St. Paul's Cray, Orpington. Chairman and Managing Director, G. H. Richards Ltd., and Synchemicals Ltd., S.E.1. *Signed by:* C. Barnett, Gordon F. Harding, T. A. Soames.

Gordon-Elliott, Augustus. British. 28, Iris Avenue, Bexley, Kent. Research and Development Chemist, Plaster Products (Greenhithe) Ltd. *Signed by:* Alfred Pass, L. O. Kekwick, S. V. Sergeant.

Grewe, Rudolf, Dr.phil. (Göttingen). German. Chemisches Institut Brunswiker Str. 2–6, Universität Kiel, Germany. Professor of Chemistry. *Signed by:* A. R. Todd, H. J. Emeléus, G. W. Kenner.

***Hopson Hill, Mrs. Betty Ida,** B.Sc. (Reading). British. 53, Alexandra Road, Reading. Research Student. *Signed by:* D. T. King, P. F. Holt, A. M. B. Whitaker.

Khoja, Mahdi Mourtadha, B.Sc. (L'pool). Iraqi. 510, Wandsworth Road, Clapham, S.W.8. Food Chemist. *Signed by:* J. A. Moss, R. O. Griffith, A. Hickling.

***Knox, John Henderson,** B.Sc. (Edin.). British. Pembroke College, Cambridge. Research Student. *Signed by:* R. G. W. Norrish, C. Kemball, J. N. Agar.

Livesey, Harold, M.A. (Cantab.). British. 33, Broadway Avenue, Wallasey. Head of Science Department, Wallasey Grammar School. *Signed by:* W. B. Whalley, R. J. S. Beer, J. Yates.

Mackie, Henry, M.Sc. and Ph.D. (Q.U.B.). British. Department of Chemistry, Queen's University, Belfast. Lecturer in Chemistry. *Signed by:* A. R. Ubbelohde, H. Graham, L. E. Sutton.

***Middlemas, John.** British. 331, Brunshaw Road, Burnley. Chemistry Student. *Signed by:* H. Hebden, D. Pedder, L. A. Whalley.

***Mieras, Alexander Adrian,** A.R.I.C. British. c/o Kuweit Oil Co. Ltd., IBI Camp, Mena-Al-Ahmadi, Kuweit, Persian Gulf. Oil Chemist. *Signed by:* A. P. Mieras, G. W. Walker, N. Campbell.

***Millard, Geoffrey Walter.** British. 17, Court Drive, Sutton. Research Student. *Signed by:* A. I. Vogel, G. H. Jeffery, J. Leicester.

Modi, Darius Tehmuras, B.Sc. (Bombay), D.Pharm. (Lond.). Indian. 17, Bloomsbury Square, London, W.C.1. Research Student. *Signed by:* A. H. Beckett, R. A. Webb, V. Askam.

***Morrill, Derek James.** British. 22, Blackthorne Grove, Bexleyheath. Research Student, University College, Southampton. *Signed by:* K. R. Webb, E. Cartmell, A. R. Burkin.

Nagdi, Khairi Ali El, B.Sc. (Fouad 1st Univ.). Egyptian. Chemistry Research Department, King's College, Strand, London, W.C.2. Research Student. *Signed by:* S. H. Harper, A. Nechvatal, A. Ashdown.

Paul, Raymoud Etienne, D.Sc. (Sorbonne). French. 16, rue Georges Guynemer, Versailles (S. et O.), France. Directeur Scientifique de la Société du Usines Chimiques Rhone-Poulenc. *Signed by:* M. Delepine, A. J. Ewins, H. King.

Robinson, Mrs. Britta Gullan. Swedish. 9, Worsley Road, London, N.W.3. Research Biochemist, The Barnato Joel Laboratory, Middlesex Hospital, W.1. *Signed by:* D. G. O'Sullivan, J. B. Jepson, W. Lawson.

***Roxburgh, Charles McCowan,** B.Sc. (Glas.), A.R.I.C. British. 11, Victoria Road, Rutherglen, Glasgow. Research Student, Glasgow University. *Signed by:* R. A. Raphael, J. D. Loudon, S. Horwood Tucker.

Simpson, George. British. 18, Selborne Road, Jordanhill, Glasgow, W.3. Senior Works Chemist, Messrs. W. B. Dick & Co. Ltd., Glasgow. *Signed by:* A. J. P. Hogg, H. R. Bentley, James Stark.

***Wade, Roy.** British. c/o Mrs. Hankinson, 44, West Crescent, Beeston, Notts. Research Student, Nottingham University. *Signed by:* F. C. Laxton, C. C. Addison, A. S. Anderson.

Walker, Garry Thomas. British. 4, Fordhook Avenue, Ealing, W.5. Assistant Chemist, Messrs. Monke and Gorton Ltd., W.6. *Signed by:* D. A. Tame, F. C. Harwood, N. A. C. Pryce.

Watson, Derek, B.Sc. (Lond.). British. Rheumatic Research Unit, Royal National Hospital for Rheumatic Diseases, Bath. Biochemist. *Signed by:* I. G. Anderson, M. E. Foss, G. Haslewood.

***Whitby, Peter Nicholas.** British. 19, Court Drive, Stanmore. Research Student, Bristol University. *Signed by:* F. H. Pollard, J. K. N. Jones, L. Hough.

Williams, Albert Frederick, B.Sc. (Lond.), F.R.I.C. British. 31, Manor Gardens, Hampton, Middlesex. Principal Scientific Officer, Chemical Research Laboratory, Teddington. *Signed by:* F. H. Burstall, G. R. Davies, R. A. Wells.

Williamson, Leonard John Anderson, F.R.I.C. British. 1, Verrill Avenue, Northenden, Manchester. Research Chemist, Hardman and Holden Ltd., Manchester. *Signed by:* H. Frankland Tucker, A. T. Royle, M. G. T. Burrows.

UNDER SPECIAL PROVISION APPERTAINING TO CANDIDATES RESIDENT ABROAD.

Anderson, Bernhardt, B.A. and Ph.D. (Wisconsin). American. University of California, Forest Products Laboratory, 243, Forestry Building, Berkeley 4, California, U.S.A. Research Biochemist. *Signed by:* Donald L. MacDonald.

Anderson, Arthur G., jun., M.S. and Ph.D. (Michigan). American. Department of Chemistry and Chemical Engineering, Bagley Hall, University of Washington, Seattle 5, Washington, U.S.A. Assistant Professor of Chemistry. *Signed by:* H. J. Daubinger, Kenneth B. Wiberg.

Baliah, Vuppalapaty, M.Sc. (Andhra), Ph.D. (Stanford). Indian. Annamalai University, Annamalainagar, South India. Professor of Chemistry. *Signed by:* T. R. Seshadri.

Bengelsdorf, Irving Swem, M.S. and Ph.D. (Chicago). American. Gates and Crellin Laboratories, California Institute of Technology, Pasadena 4, California, U.S.A. Research Fellow. *Signed by:* Stanley L. Cosgrove.

Buc, Saul R., B.S. (Rutgers), Ph.D. (Johns Hopkins). American. R.D. 4, Easton, Pennsylvania, U.S.A. Research Chemist, General Aniline and Film Corporation. *Signed by:* W. L. Mosby.

Chê, John Man Mo, B.Sc. (Sun Yat San Univ.). British. 32, Tung Lo Wan Road, Top Floor, Causeway Bay, Hong Kong. Chemist, L. Aine & Co. (H.K.). *Signed by:* E. Collins.

de Jong, Frans Peter Karel. Dutch. Bibliotheek Staatsmijnen in Limburg, Geleen, Holland. Engineer. *Signed by:* F. R. Schepman.

***Jennings, Keith Frandor.** British. Department of Chemistry, University of Western Ontario, London, Canada. Research Student. *Signed by:* F. L. M. Pattison.

Kohn, Leon, B.Chem.Eng. (City Coll. of New York), M.S. (Oklahoma A. & M. Coll.). American. 210, Waldron Street, W. Lafayette, Indiana, U.S.A. Research Student. *Signed by:* M. Seidman.

Kreiter, Victor Peter, jun., M.S. (Michigan). American. 5, Fayette Street, Hillsdale, Michigan, U.S.A. Graduate Student, Stanford University. *Signed by:* Gene Kritchevsky, Phillip M. Iloff, jun.

Kuntz, Irving, M.S. (Polytechnic Inst. of Brooklyn). American. 67, Cherry Street, North Adams, Massachusetts, U.S.A. Research Chemist, Sprague Electric Co., North Adams. *Signed by:* F. M. Beringer.

***Nelson, Peter Frederick,** M.Sc. (Melbourne). British. Flat 5, 352, Albert Road, South Melbourne, Victoria, Australia. Lecturer, Melbourne Technical College. *Signed by:* S. F. Cox, L. R. Wilkinson.

Petit, André Victor, Chem.Eng. (Paris). French. 71, Avenue de Breteuil, Paris 15e, France. Chief of Research Department, Usines Chimiques des Laboratoires Français. *Signed by:* C. W. Shoppee.

Rapkin, Edward, M.S. and Ph.D. (Purdue). American. Armour Research Foundation, Illinois Institute of Technology, Technology Centre, Chicago, Illinois, U.S.A. Research Organic Chemist. *Signed by:* N. Kornblum, J. H. Brewster.

Ross, Sidney David, M.A. (Boston), Ph.D. (Harvard). American. 142, Main Street, Williamstown, Massachusetts, U.S.A. Director of Organic Chemical Research, Sprague Electric Co., North Adams. *Signed by:* F. M. Beringer.

***Segal, Wolfe,** M.Sc. (Melbourne). Australian. 200, Scotchmen Street, North Fitzroy, N.7, Victoria, Australia. Research Student, Melbourne University. *Signed by:* N. V. Riggs.

Shaw, Kenneth Noel Francis, M.A. (British Columbia), Ph.D. (Iowa State Coll.). Canadian. Department of Chemistry, Iowa State College, Ames, Iowa, U.S.A. Research Graduate Assistant. *Signed by:* George S. Hammond.

Singleton, Philip A., LL.B. (Yale). American. 8, Waterloo Place, London, S.W.1. Assistant to Managing Director, Monsanto Chemicals Ltd. *Signed by:* J. W. Barrett, Eric K. Rideal.

* Reduced annual subscription.

PAPERS RECEIVED

(List of papers received between March 18th and April 19th, 1951.)

"The liquid dinitrogen tetroxide solvent system. Part VII. Products of reaction of zinc with liquid dinitrogen tetroxide." By C. C. ADDISON, J. LEWIS, and R. THOMPSON.

"The liquid dinitrogen tetroxide solvent system. Part VIII. Rates, and possible mechanisms, of reaction of zinc with liquid dinitrogen tetroxide." By C. C. ADDISON and J. LEWIS.

"Adsorption of the aliphatic acids—acetic to octanoic—at the nitromethane solution–air interface." By D. C. JONES and L. SAUNDERS.

"Magnetochemistry of the heaviest elements. Part IV. Plutonium trifluoride and trichloride." By J. K. DAWSON, C. J. MANDLEBERG, and D. DAVIES.

" The chemotherapy of tuberculosis. Part III. Some *N*-substituted 4-aminodiphenyls." By L. BAUER, J. CYMERMAN, and W. J. SHELDON.
" The mesomerism of keten and three of its derivatives." By C. L. ANGYAL, C. A. BARCLAY, A. A. HUKINS, and R. J. W. LEFÈVRE.
" Nucleotides. Part VII. Analogues of adenosine-5' phosphate and uridine-5' phosphate containing phenylphosphonate and ethyl phosphonate groups." By N. ANAND and A. R. TODD.
" The hydrolysis of arylsulphonic esters. Part I." By C. A. BUNTON and (MRS.) Y. F. FREI.
" Deoxy-sugars. Part XXII. Comparative rates of oxidation and reduction of D-galactose and 2-deoxy-D-galactose." By W. G. OVEREND, F. SHAFIZADEH, and M. STACEY.
" The influence of mixed solvents on the ionisation of silver acetate." By P. B. DAVIES and C. B. MONK.
" The influence of mixed solvents on the solubilities of salts." By C. B. MONK.
" 3 : 4-Benzoxanthens. Part II. The synthesis of 5-, 6-, and 7-methyl-3 : 4-benzoxanthones." By M. GINDY and I. W. DWIDAR.
" The preparation and heats of combustion of some amine nitrates." By T. L. COTTRELL and J. E. GILL.
" The synthesis and reactions of branched-chain hydrocarbons. Part I. Hydrocarbons with the 3 : 5 : 5-trimethylhexyl group." By E. M. GUTMAN and W. J. HICKINBOTTOM.
" 2-Mercaptoglyoxalines. Part I. The synthesis of ergothioneine." By H. HEATH, A. LAWSON, and C. RIMINGTON.
" 2-Mercaptoglyoxalines. Part II. Application of the Mannich reaction. Protection of the thiol group." By H. HEATH, A. LAWSON, and C. RIMINGTON.
" 2-Mercaptoglyoxalines. Part III. Synthesis of 2-mercapto-4(5)-methylhistidine and 4-methylergothioneine." By H. HEATH, A. LAWSON, and C. RIMINGTON.
" 2-Mercaptoglyoxalines. Part IV. Bromination with *N*-bromosuccinimide. The Reimer–Tiemann reaction." By H. HEATH, A. LAWSON, and C. RIMINGTON.
" Inhibitors of flavoprotein enzymes." By R. B. BARLOW.
" Synthesis of deoxy*apo*xanthoxyletin." By A. ROBERTSON and W. B. WHALLEY.
" The chemistry of fungi. Part XV. The degradation of methyl *O*-dimethylcitromycetin." By A. ROBERTSON, W. B. WHALLEY, and J. YATES.
" The chemistry of Fungi. Part XVI. Eburicoic acid." By R. M. GASCOIGNE, J. S. E. HOLKER, B. J. RALPH, and A. ROBERTSON.
" The chemistry of the melanins. Part III. The synthesis of hydroxyindoles from *p*-benzoquinones." By R. J. S. BEER, K. CLARKE, H. F. DAVENPORT, and A. ROBERTSON.
" Rottlerin. Part VIII. The rottlerone change." By A. MCGOOKIN, A. ROBERTSON, and T. H. SIMPSON.
" Some alkylresorcinols." By J. P. BROWN, D. H. JOHNSON, A. ROBERTSON, and W. B. WHALLEY.
" A Note on Huttig's multilayer isotherm." By R. M. BARRER.
" Infra-red carbonyl absorptions. Part I. Acyl peroxides." By W. H. T. DAVISON.
" Ion association in aqueous solutions of metal dicarboxylates." By J. M. PEACOCK and J. C. JAMES.
" An aldehyde of the phenothiazine series." By NG. PH. BUU-HOÏ and NG. HOÁN.
" The localization theory of organic reactions. Part I. The effects of annelation and of introduction of hetero-atoms." By R. D. BROWN.
" Preparation of pyridinobenziminazole and its derivatives." By N. CAMPBELL and E. B. MCCALL.
" Elimination reactions. Part I. Acid-catalysed enolisation and substitution reactions of ketones." By H. M. E. CARDWELL and A. E. KILNER.
" Elimination reactions. Part II. Base-catalysed ionisation and substitution reactions of ketones and nitroparaffins." By H. M. E. CARDWELL.

" The isomerisation of diallyl sulphilimines." By A. S. F. Ash, F. Challenger, and D. Greenwood.
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